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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone, ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] Therefore clinicians have three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms.[41]

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (Figure 4). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 5 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. Figure 6 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 7 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (Figure 8). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone and ranibizumab,[18 19] and is currently appraising aflibercept. Until these technologies are reviewed together and compared with each other, clinicians may be left with three recommended drugs for macular oedema secondary to central retinal vein occlusion. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because it costs substantially

less.[57] However the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months					
Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA					
Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-up

Figure 1: study selection flow diagram

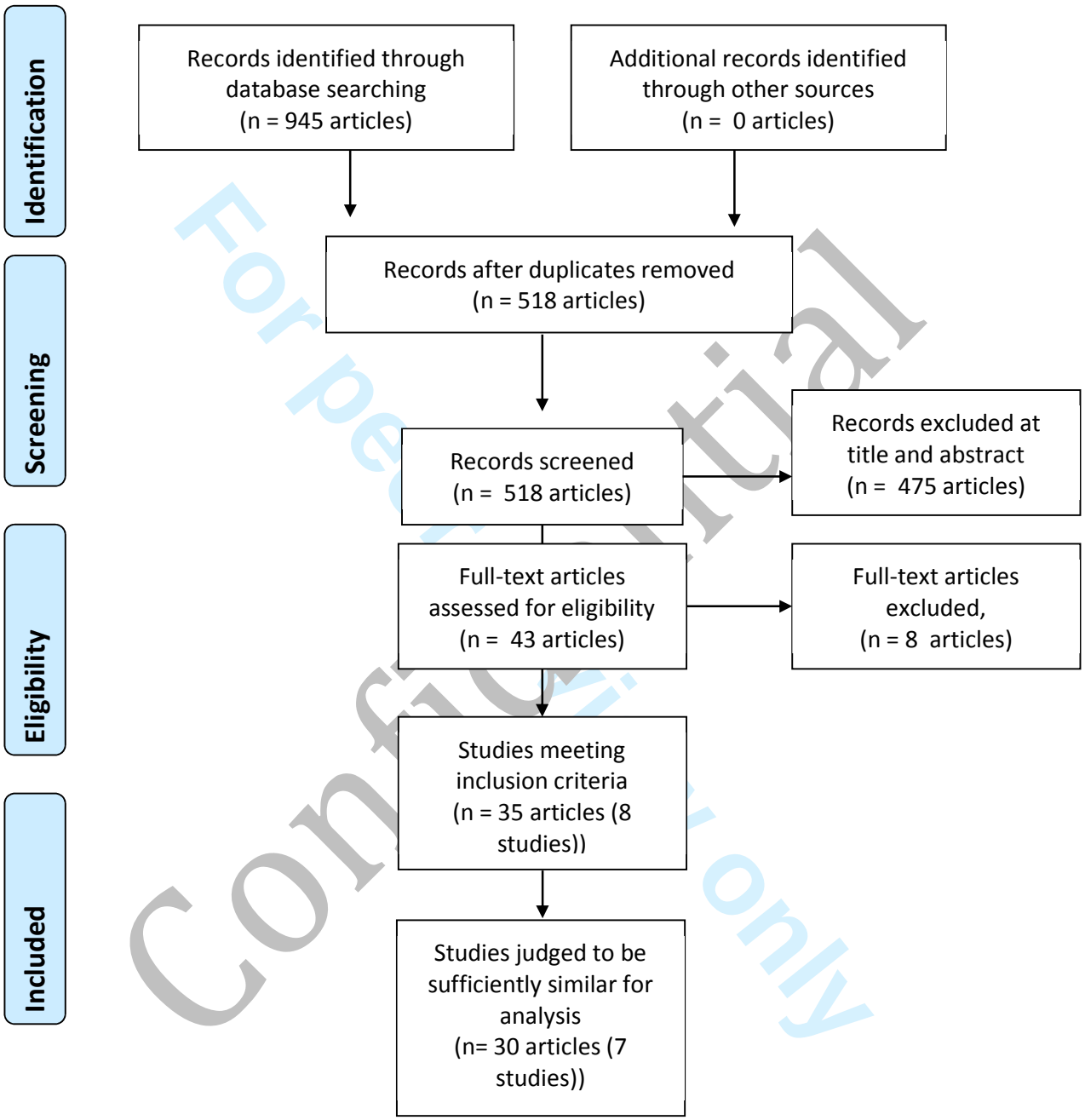


Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

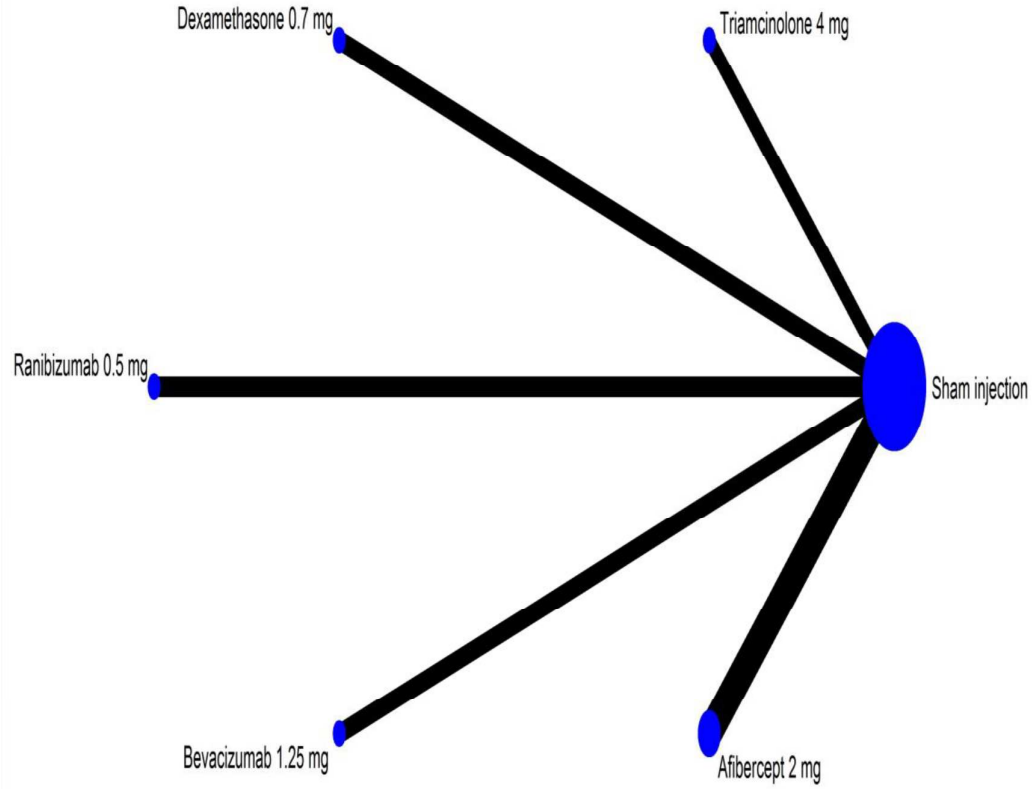


Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

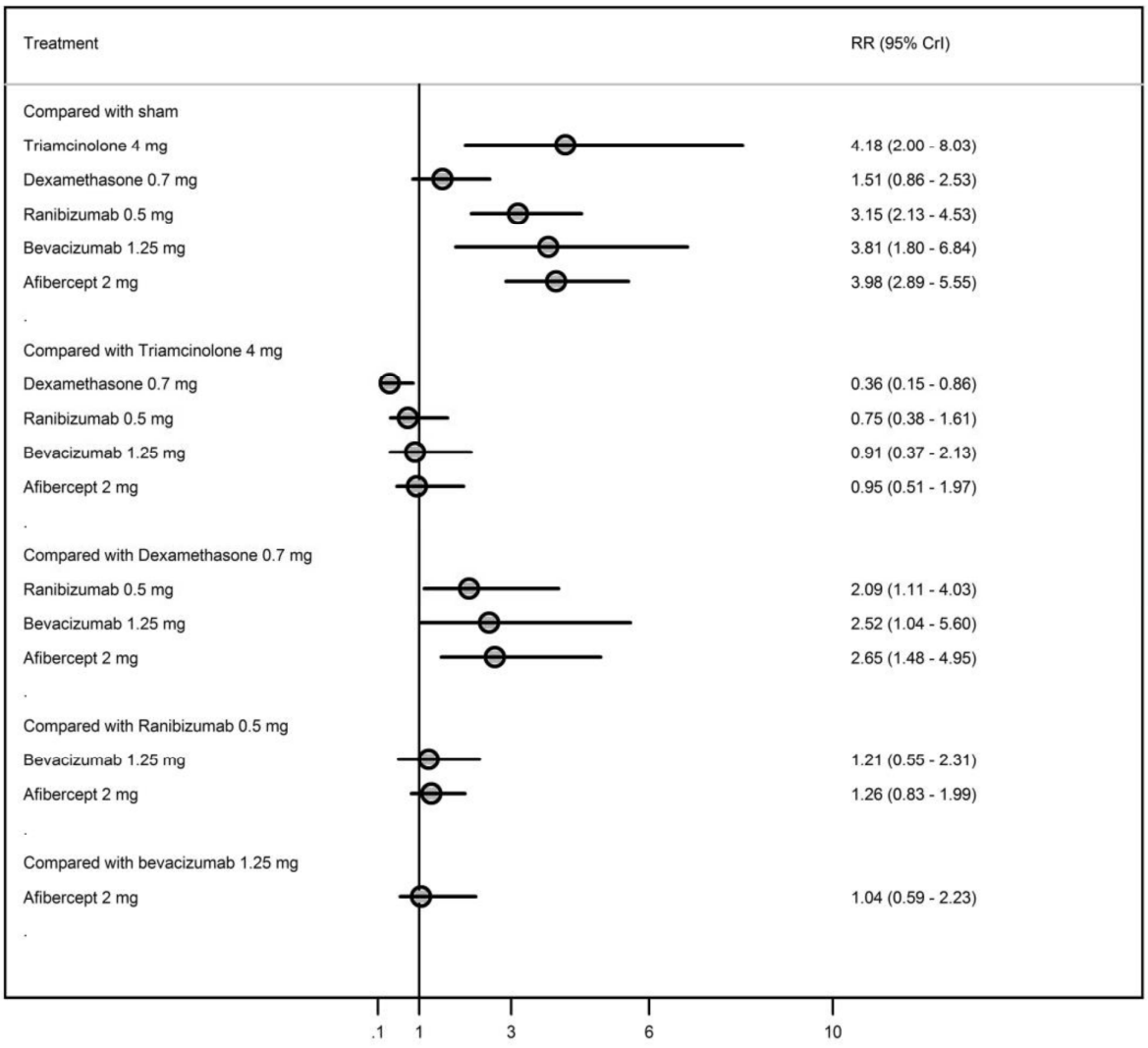


Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

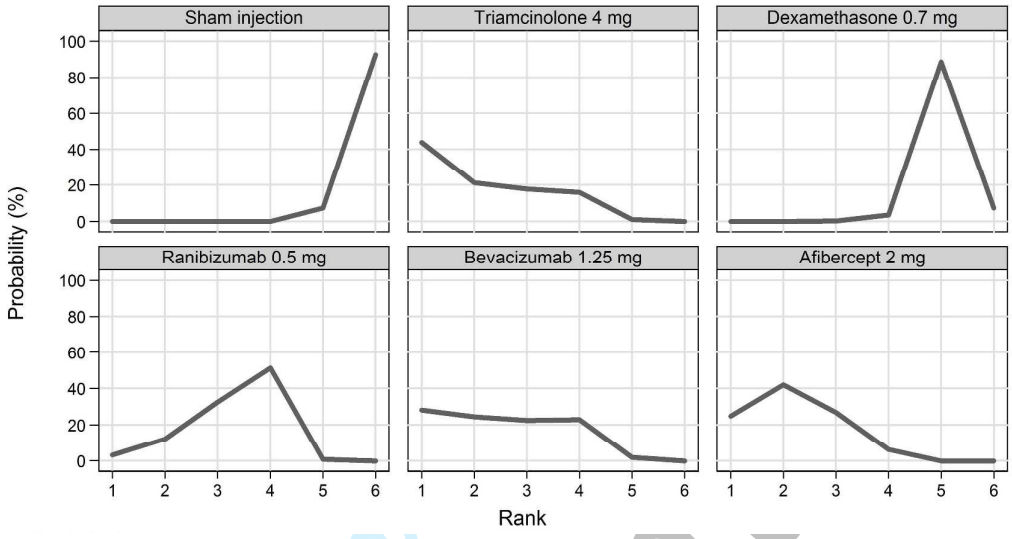


Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

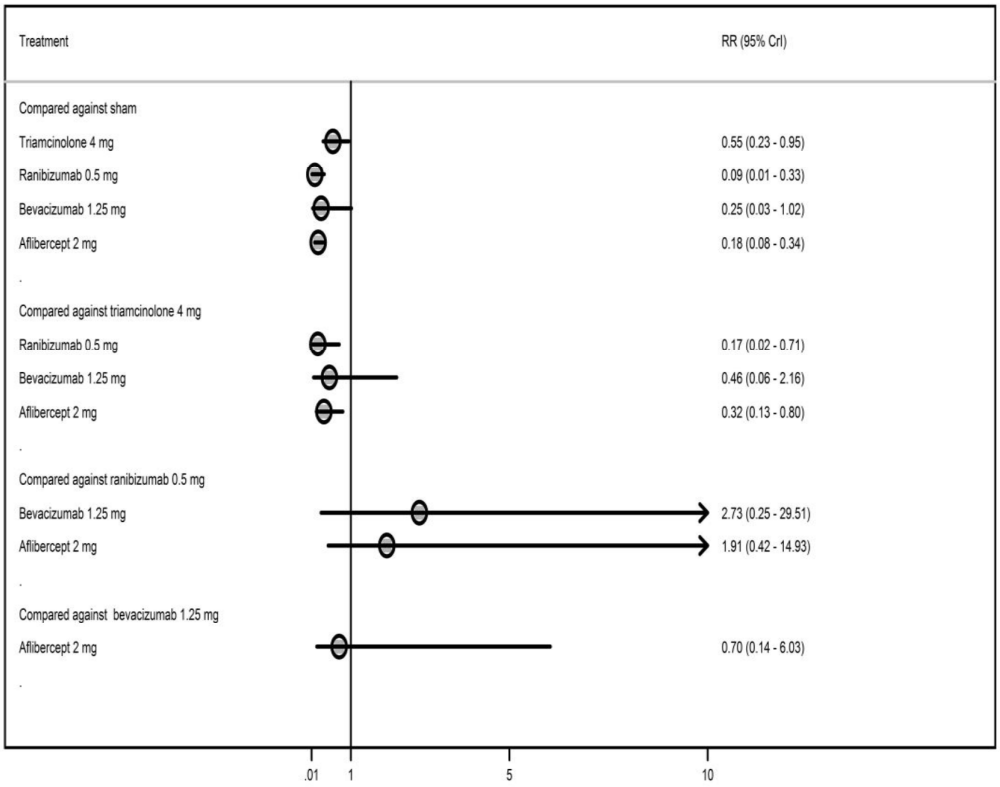


Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

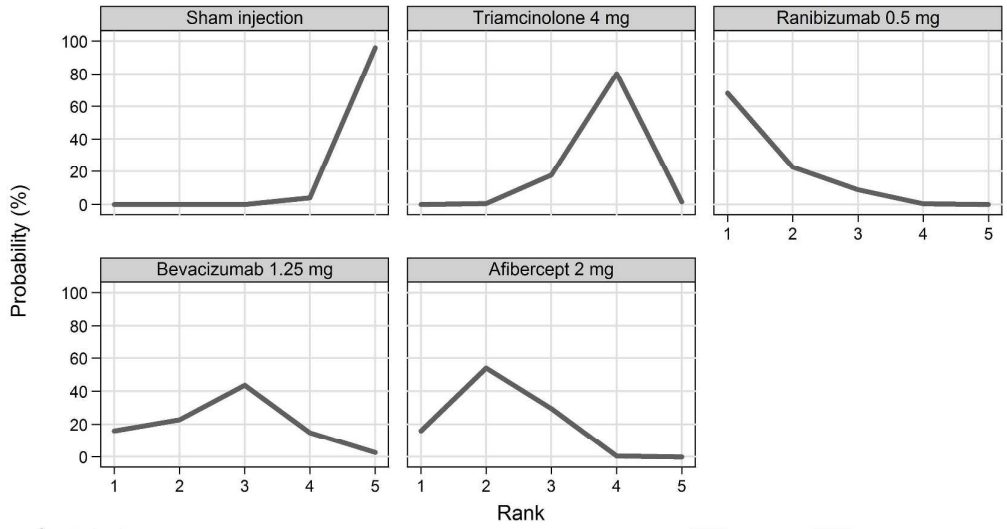


Figure 7: Mean BCVA change from baseline to 6 months.

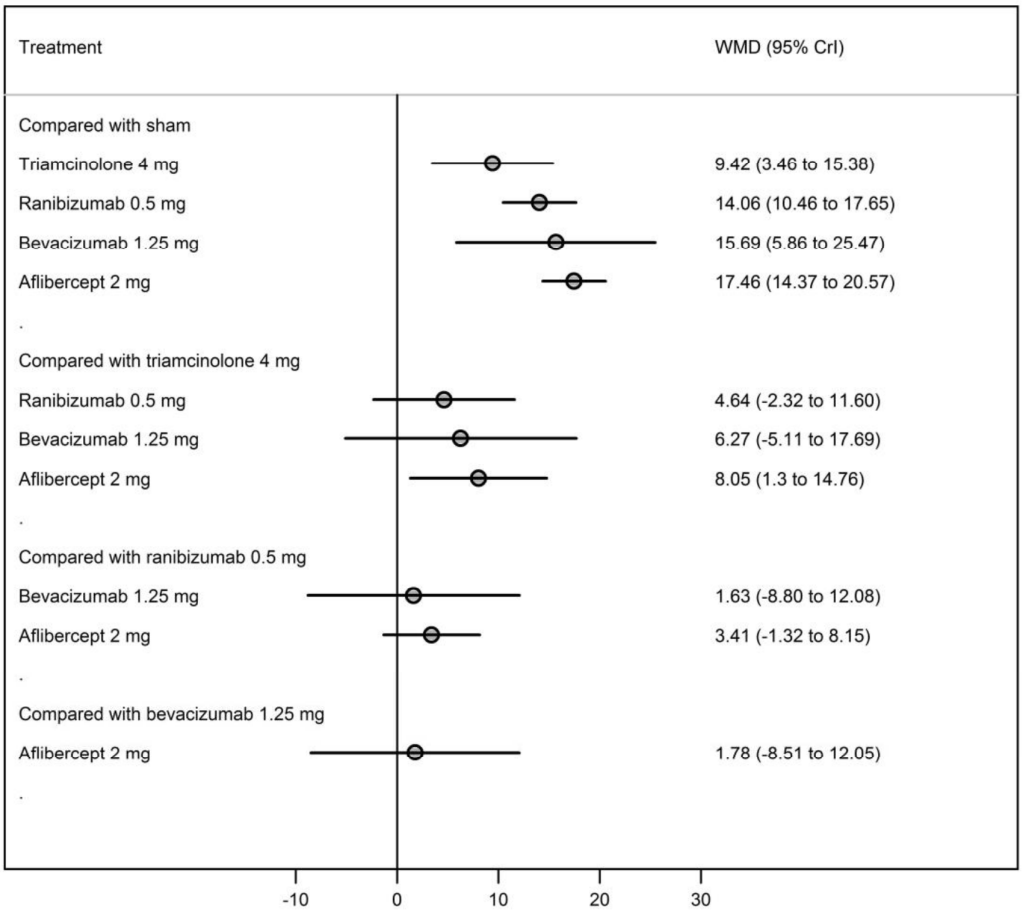
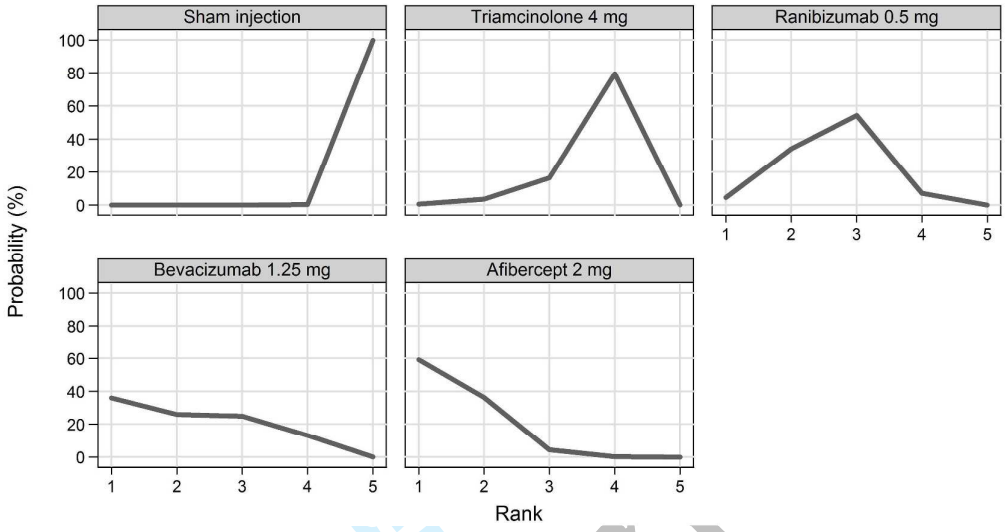


Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions



Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.
2 Retinal Vein Occlusion/
3 retinal vein occlusion.mp.
4 retinal vein obstruction.mp.
5 retinal venous occlusion.mp.
6 retinal venous obstruction.mp.
7 retina*.mp.
8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
9 7 and 8
10 1 or 2 or 3 or 4 or 5 or 6 or 9
11 randomized controlled trial.pt.
12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
13 11 or 12
14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
15 "systematic review*".tw.
16 meta analysis.pt.
17 14 or 15 or 16
18 10 and 13
19 10 and 17
20 18 or 19
21 limit 20 to yr="2005 -Current"

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	41
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11+27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25-26
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	29-31
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone~~, and~~ ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] ~~and it is currently evaluating aflibercept. If aflibercept is also endorsed and with no head-to-head trials comparing these drugs,~~ Therefore clinicians ~~will be in the position of~~ hav~~e~~ing three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms. ~~(Salanti)~~[41].

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (eFigure 41). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 54 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. eFigure 62 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 75 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (eFigure 83). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone and ranibizumab,[18 19] and is currently appraising aflibercept. Until these technologies are reviewed together and compared with each other, clinicians may be left with three recommended drugs for macular oedema secondary to central retinal vein occlusion. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because it costs substantially

less.[57] However the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

	Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months						
	Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA						
	Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-up

Figure 1: study selection flow diagram

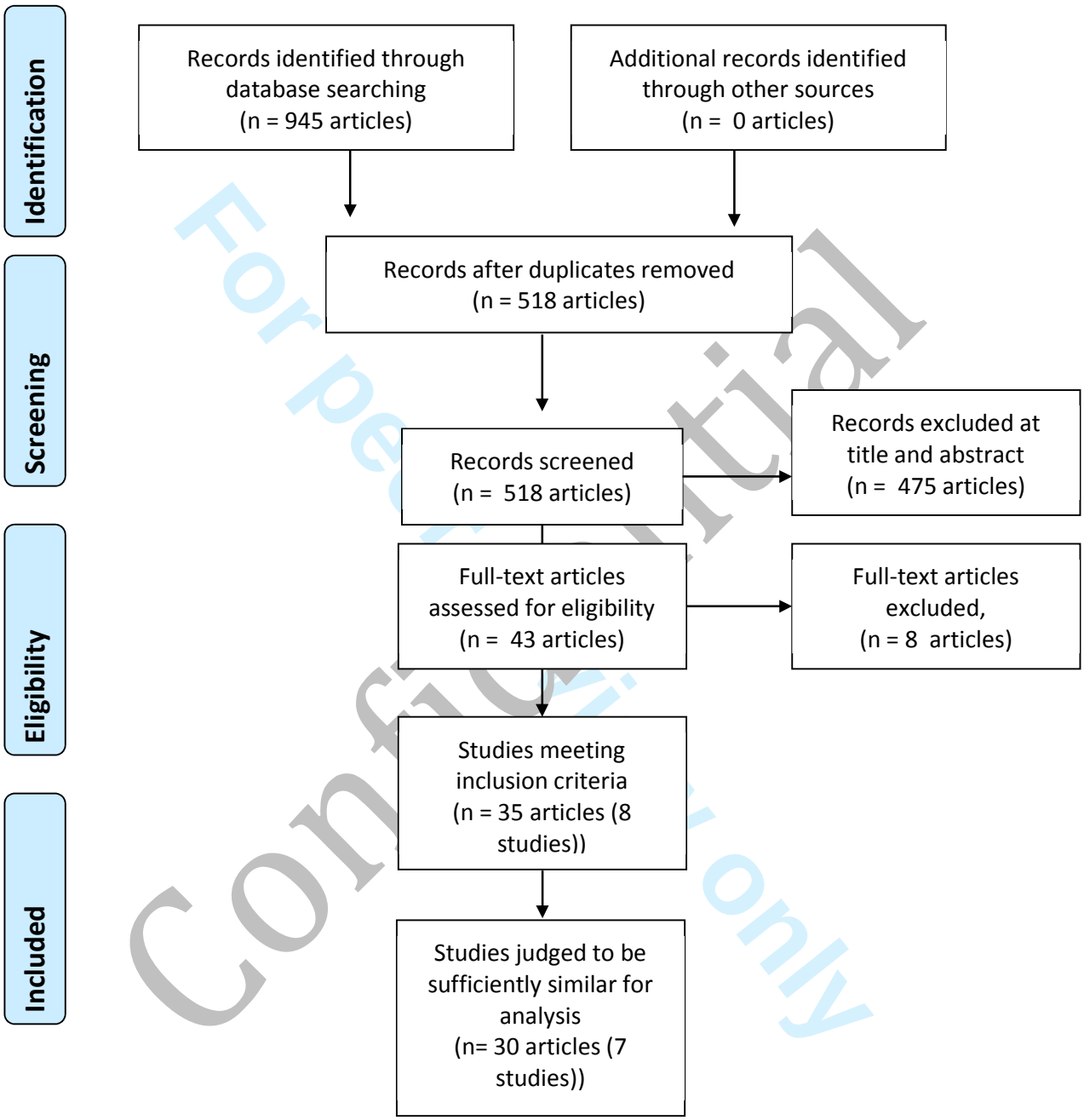


Figure 2: Network of randomized controlled trials comparing different

Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

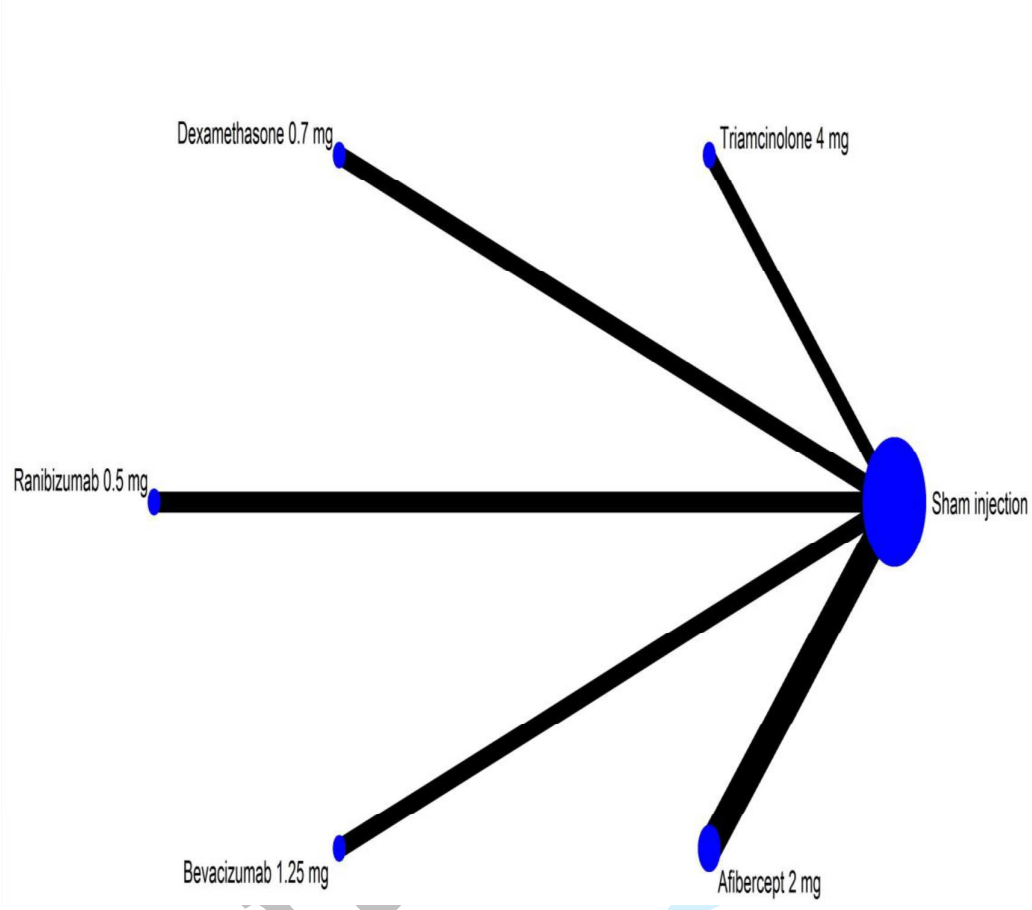


Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

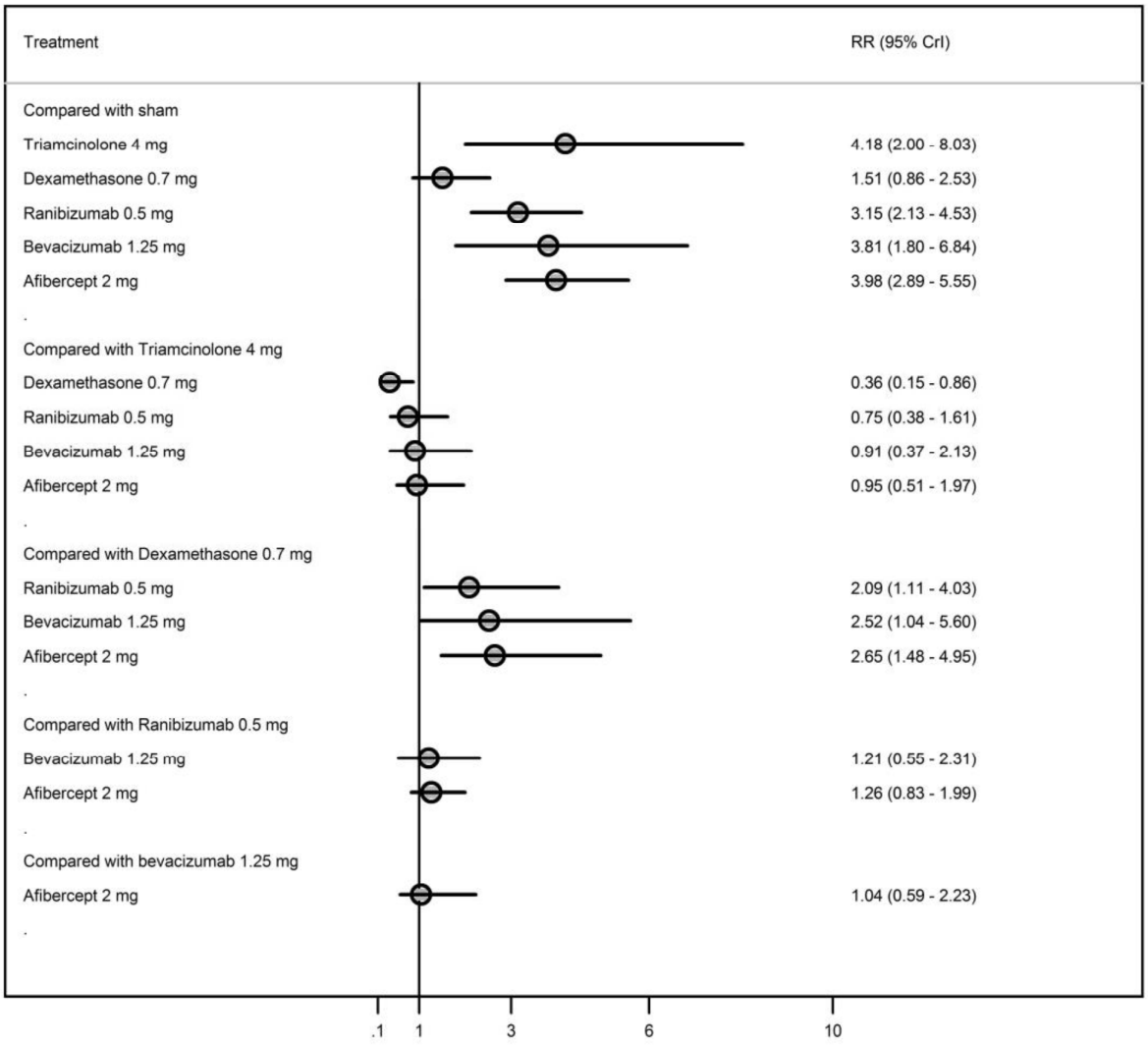


Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

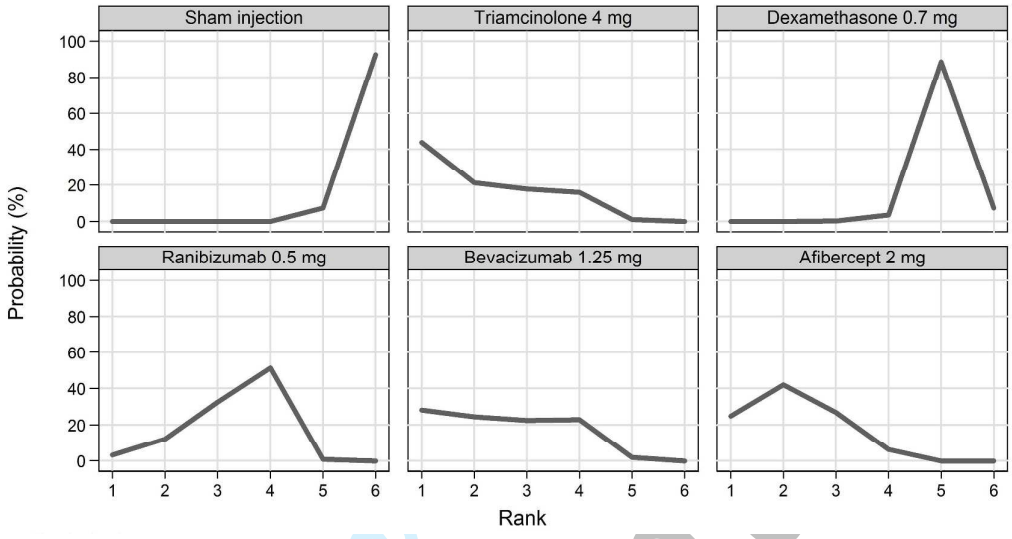


Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

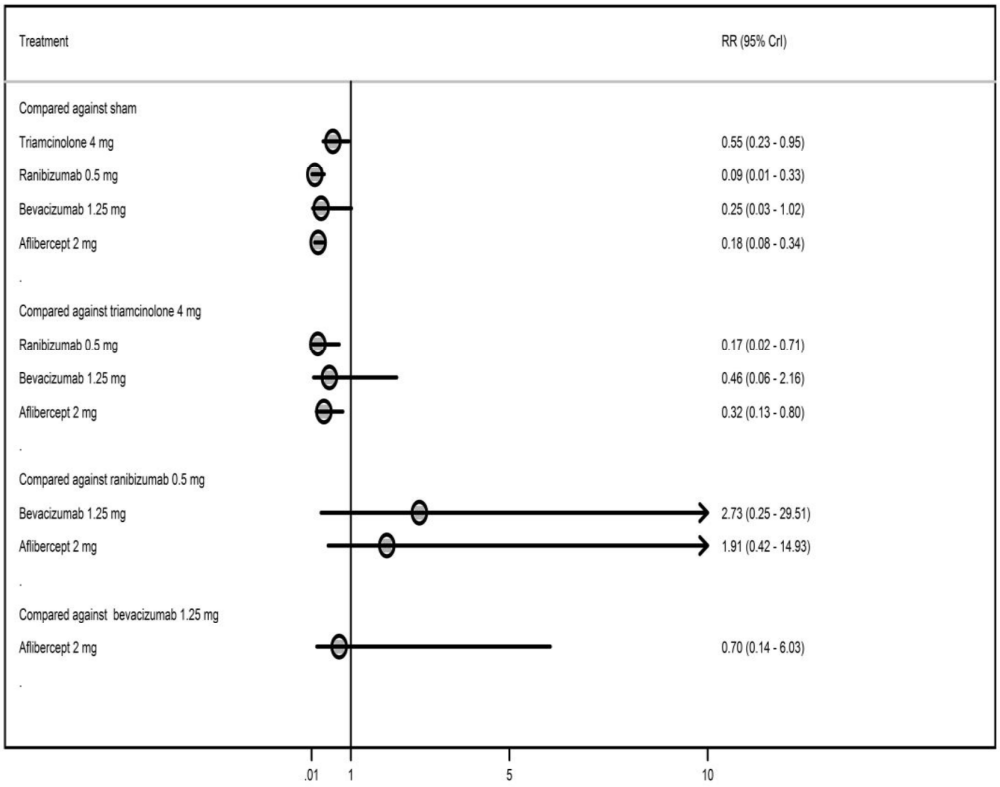


Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

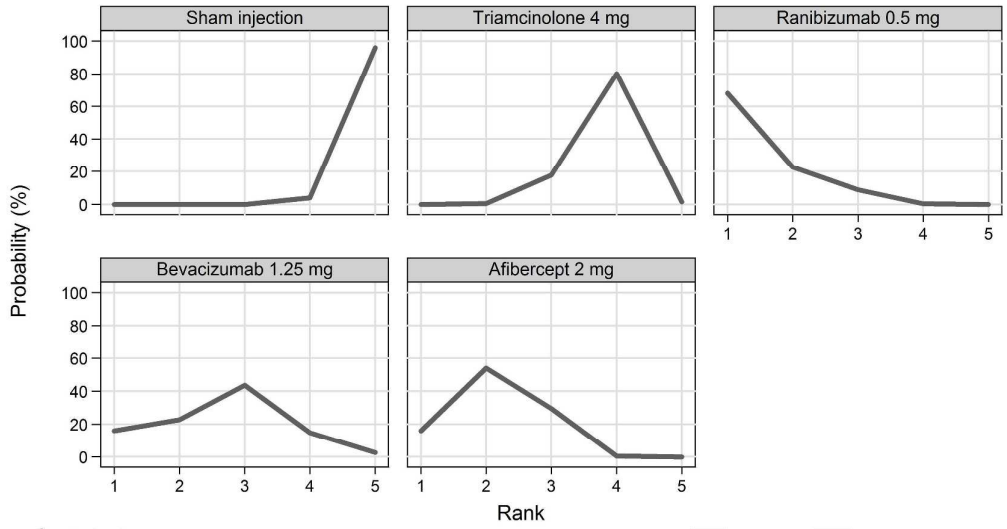


Figure 7: Mean BCVA change from baseline to 6 months.

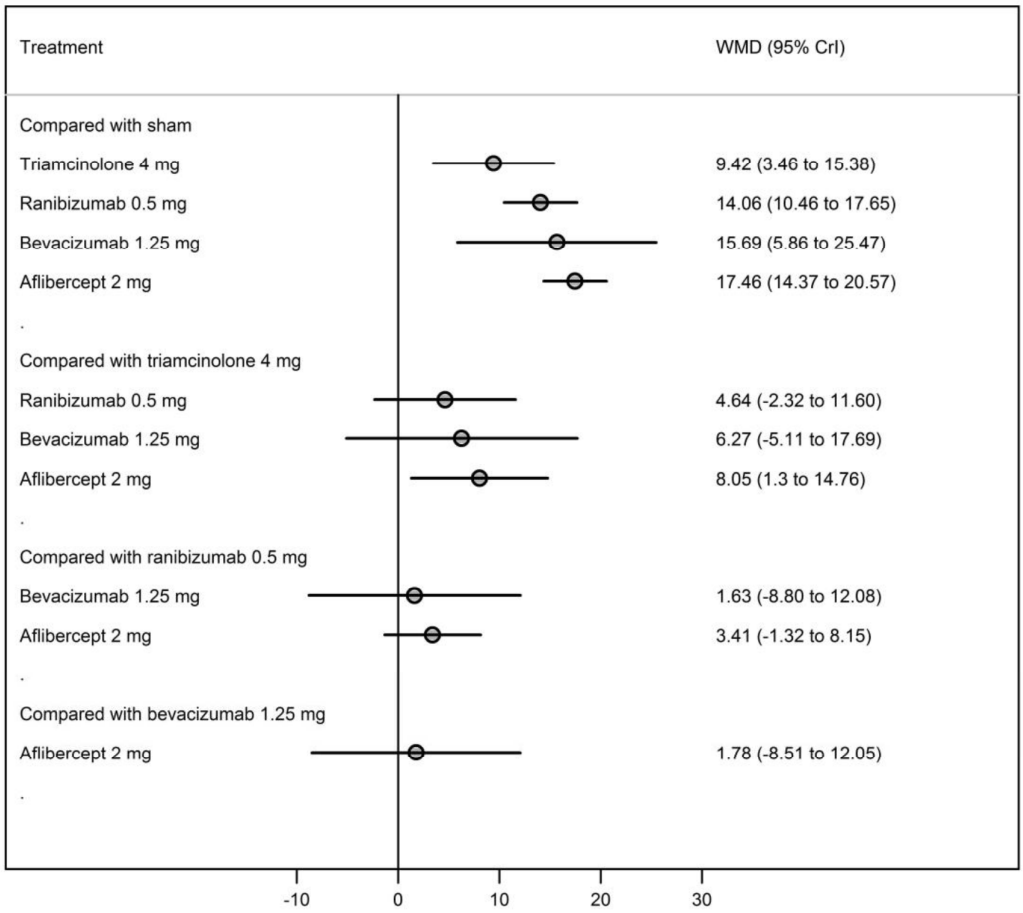
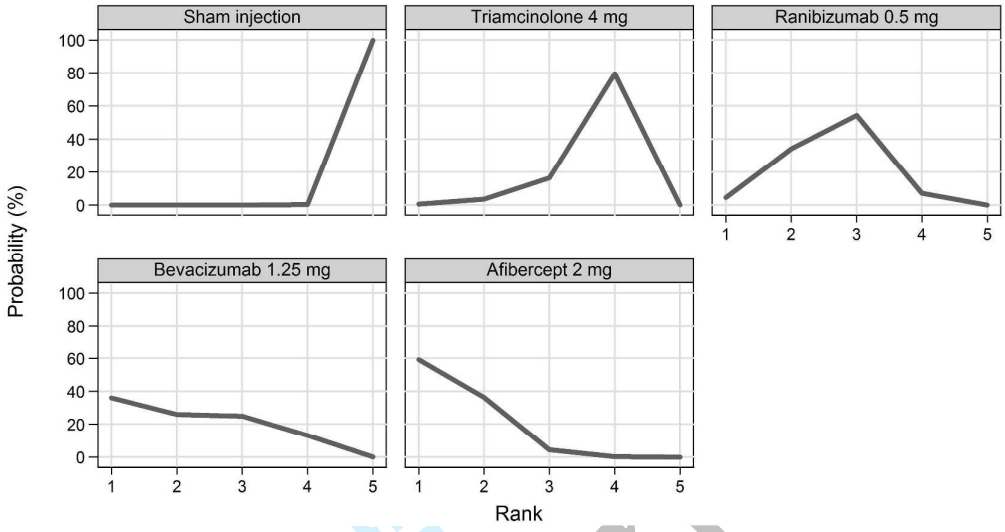


Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions



Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.
2 Retinal Vein Occlusion/
3 retinal vein occlusion.mp.
4 retinal vein obstruction.mp.
5 retinal venous occlusion.mp.
6 retinal venous obstruction.mp.
7 retina*.mp.
8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
9 7 and 8
10 1 or 2 or 3 or 4 or 5 or 6 or 9
11 randomized controlled trial.pt.
12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
13 11 or 12
14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
15 "systematic review*".tw.
16 meta analysis.pt.
17 14 or 15 or 16
18 10 and 13
19 10 and 17
20 18 or 19
21 limit 20 to yr="2005 -Current"

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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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Data sharing: no additional data available

Word count: 3,331 words

What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone, ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] Therefore clinicians have three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms.[41]

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (Figure 4). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 5 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. Figure 6 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 7 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (Figure 8). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone and ranibizumab,[18 19] and is currently appraising aflibercept. Until these technologies are reviewed together and compared with each other, clinicians may be left with three recommended drugs for macular oedema secondary to central retinal vein occlusion. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because it costs substantially

less.[57] However the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months					
Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA					
Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-up

Figure 1: study selection flow diagram

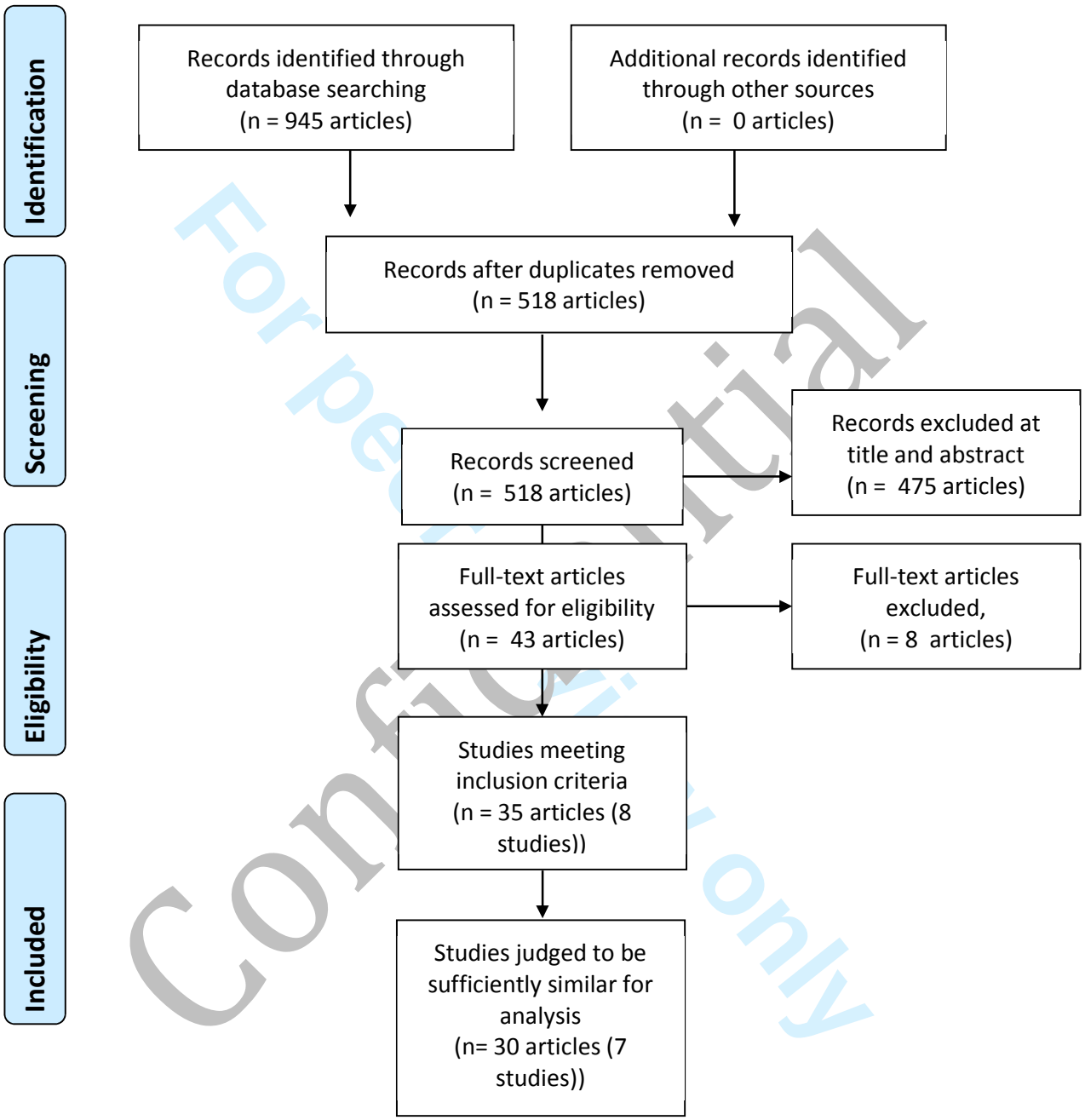


Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

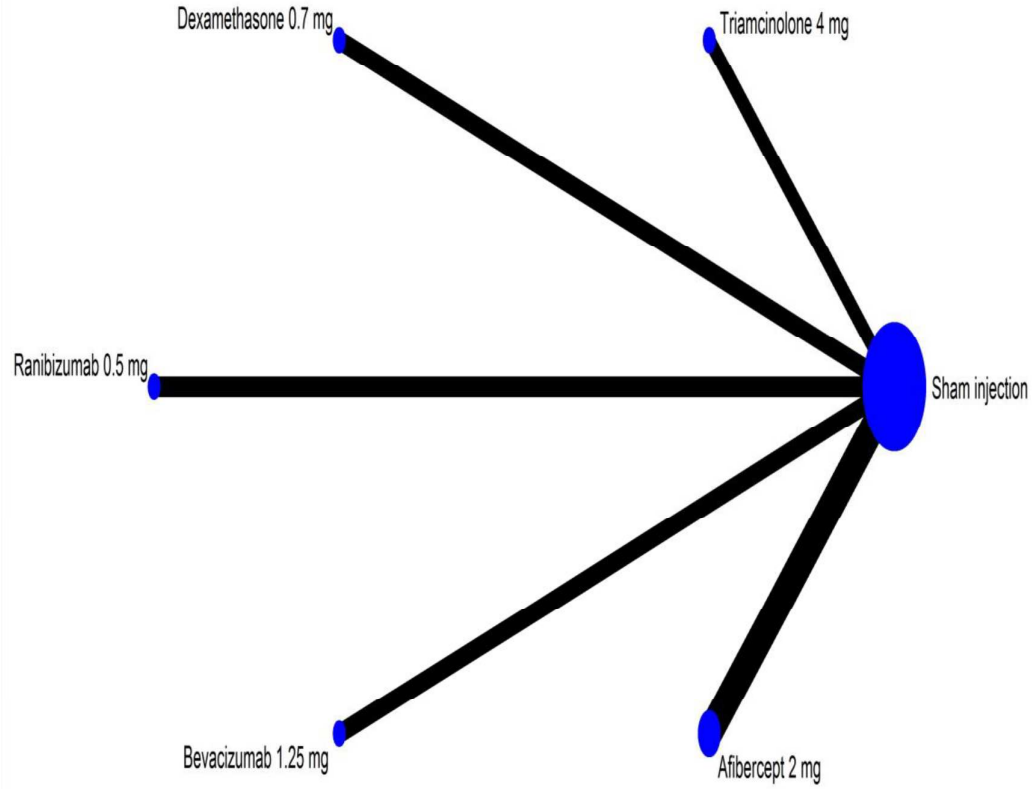


Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

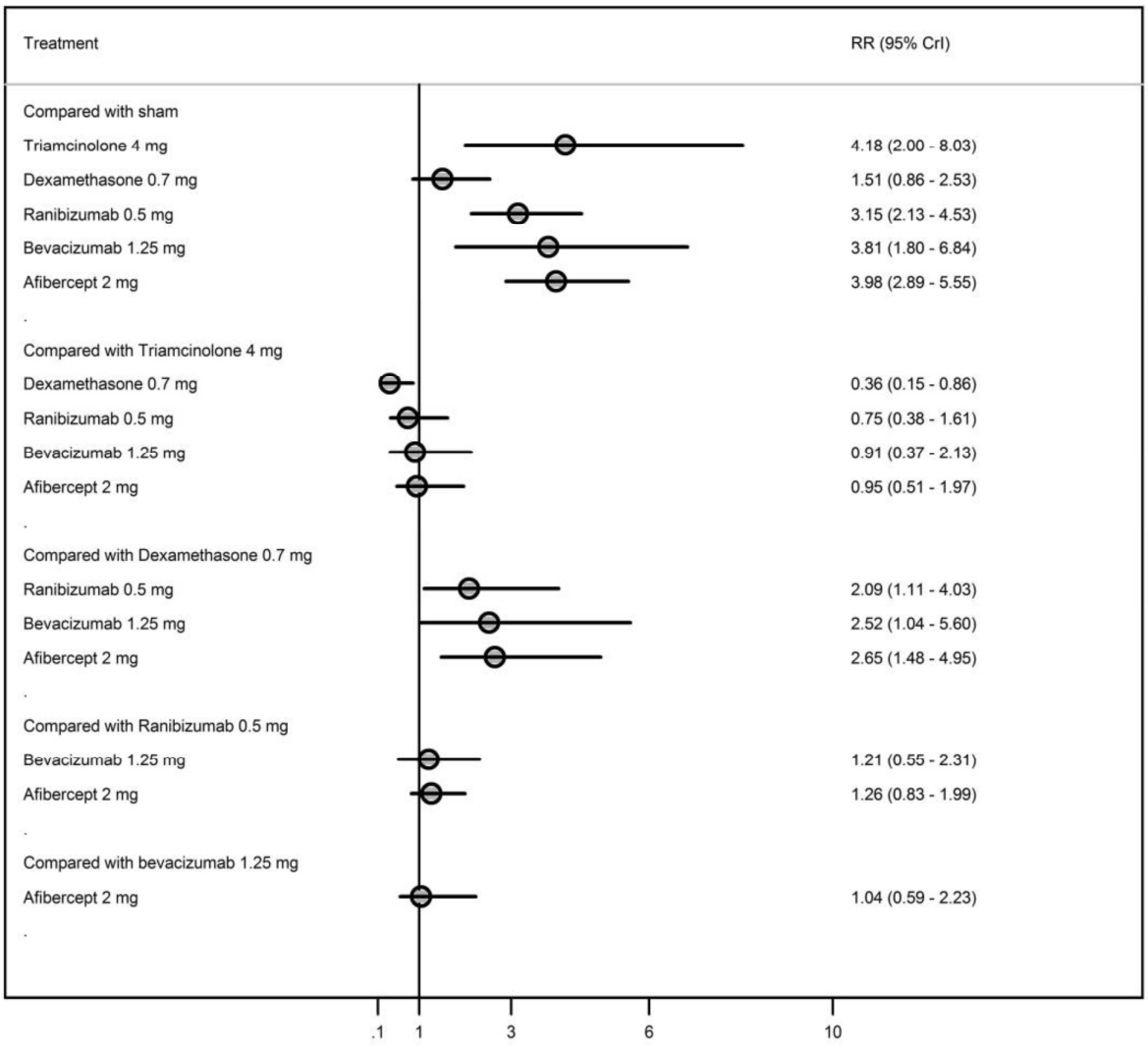


Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

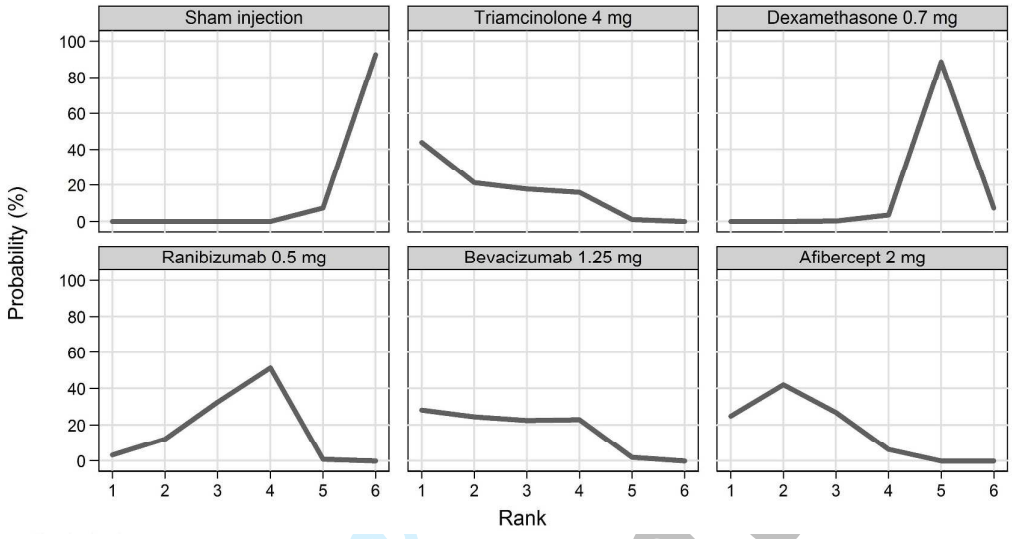


Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

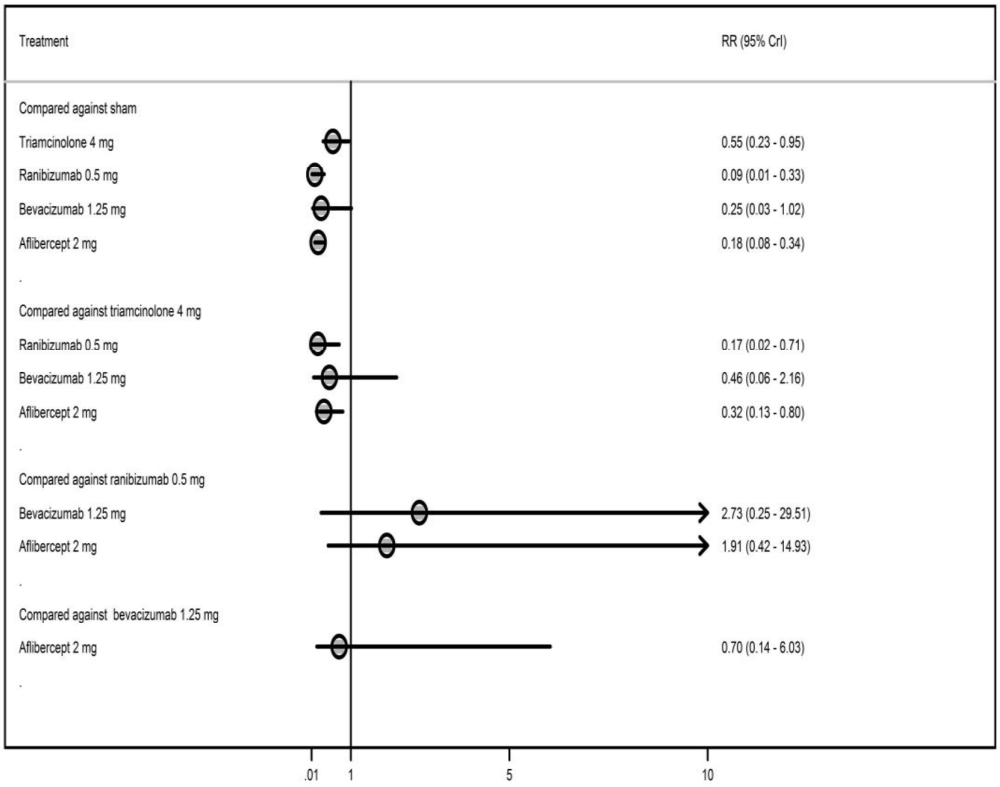


Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

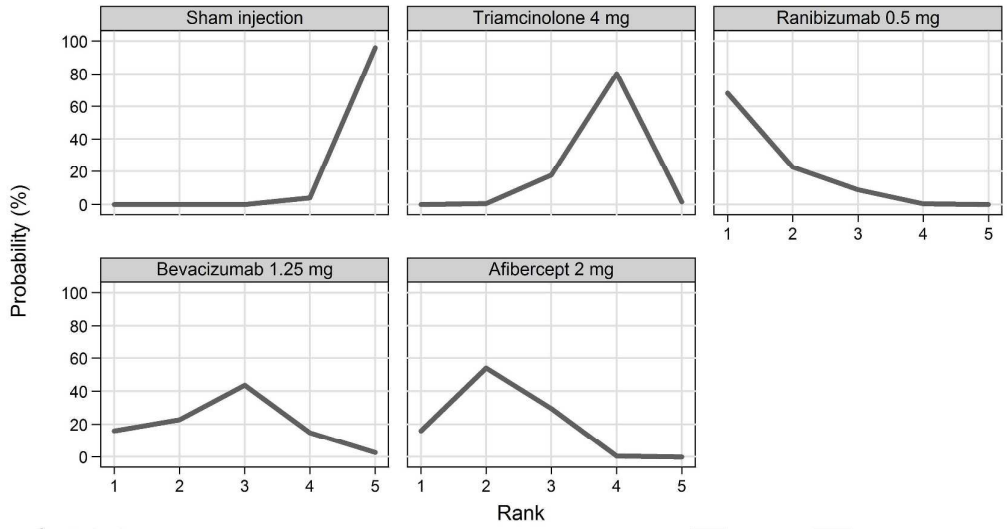


Figure 7: Mean BCVA change from baseline to 6 months.

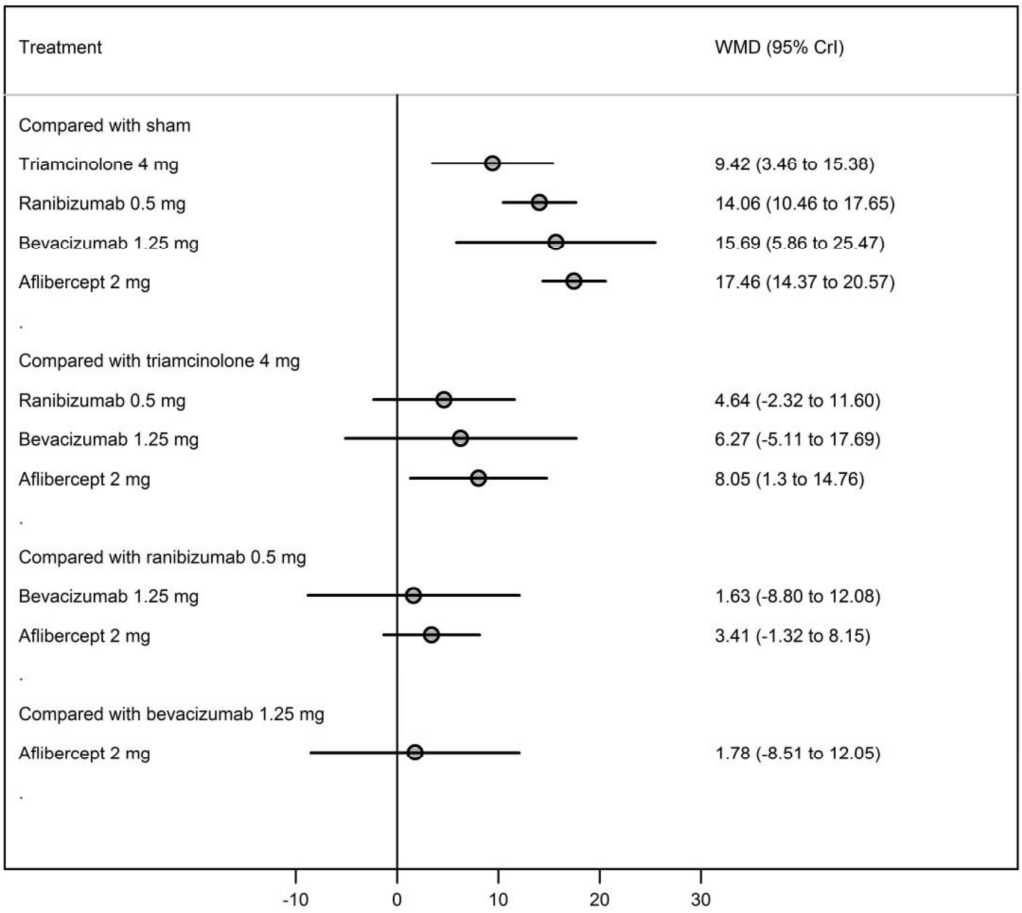
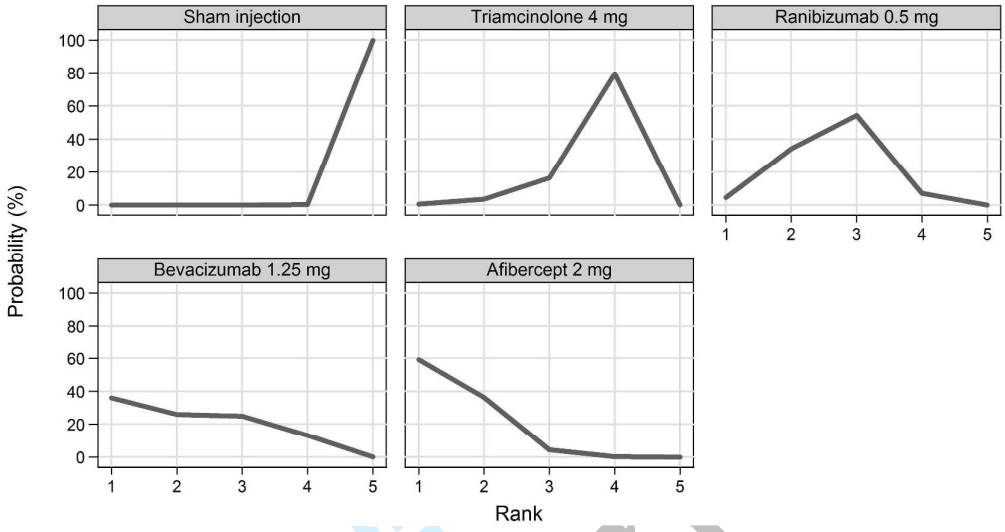


Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions



Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.
2 Retinal Vein Occlusion/
3 retinal vein occlusion.mp.
4 retinal vein obstruction.mp.
5 retinal venous occlusion.mp.
6 retinal venous obstruction.mp.
7 retina*.mp.
8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
9 7 and 8
10 1 or 2 or 3 or 4 or 5 or 6 or 9
11 randomized controlled trial.pt.
12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
13 11 or 12
14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
15 "systematic review*".tw.
16 meta analysis.pt.
17 14 or 15 or 16
18 10 and 13
19 10 and 17
20 18 or 19
21 limit 20 to yr="2005 -Current"

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	41
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11+27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25-26
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	29-31
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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Protocol – no published protocol exists for this study.

Ethics approval – not required

Funding – no external funding required

Data sharing: no additional data available

Word count: 3,331 words

What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone~~, and~~ ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] ~~and it is currently evaluating aflibercept. If aflibercept is also endorsed and with no head-to-head trials comparing these drugs,~~ Therefore clinicians ~~will be in the position of~~ hav~~e~~ing three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms. ~~(Salanti)~~[41].

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (eFigure 41). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 54 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. eFigure 62 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 75 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (eFigure 83). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone and ranibizumab,[18 19] and is currently appraising aflibercept. Until these technologies are reviewed together and compared with each other, clinicians may be left with three recommended drugs for macular oedema secondary to central retinal vein occlusion. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because it costs substantially

less.[57] However the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

	Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months						
	Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA						
	Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-up

Figure 1: study selection flow diagram

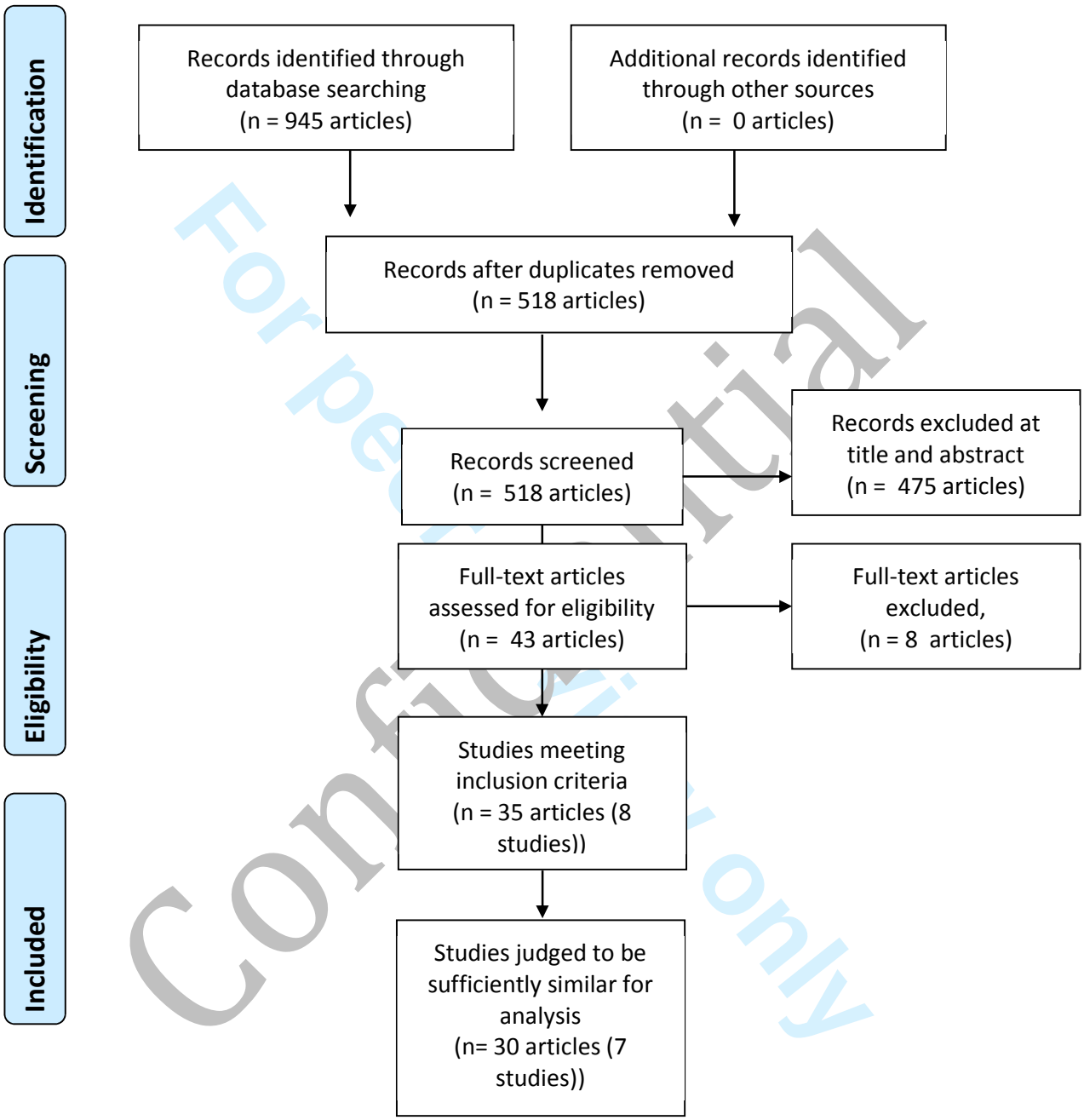


Figure 2: Network of randomized controlled trials comparing different

Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

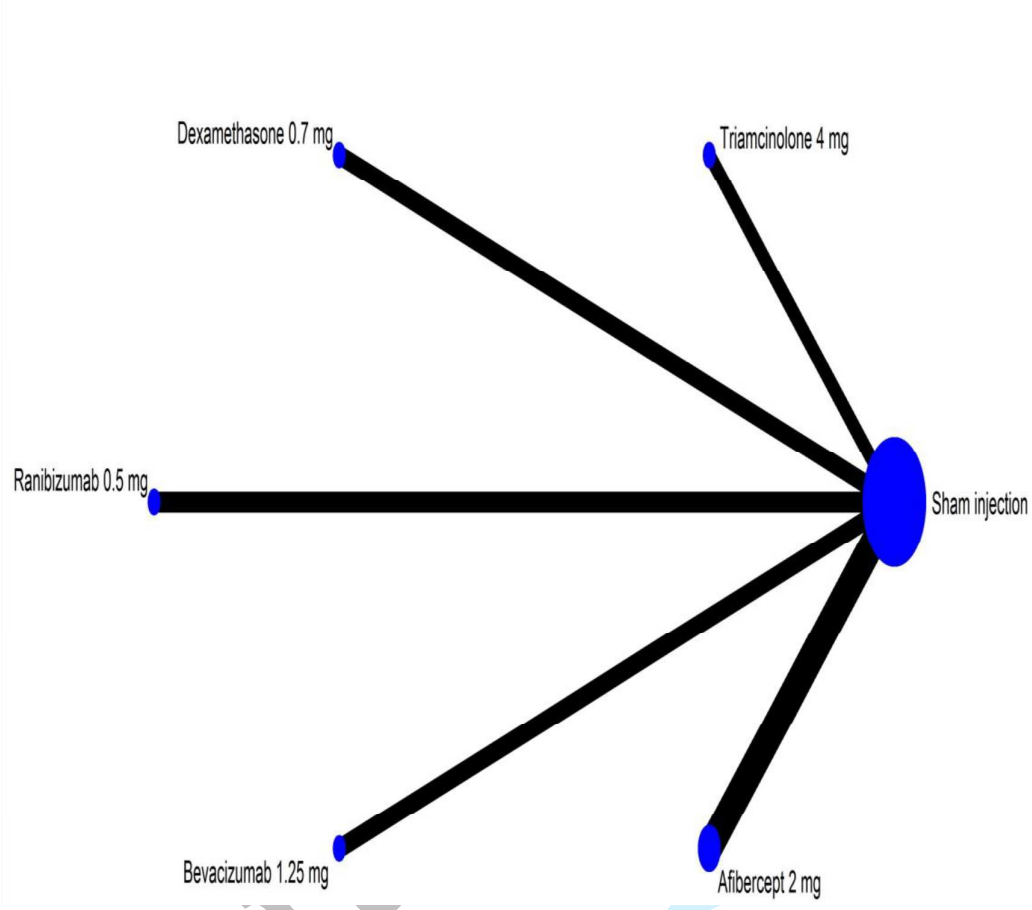


Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

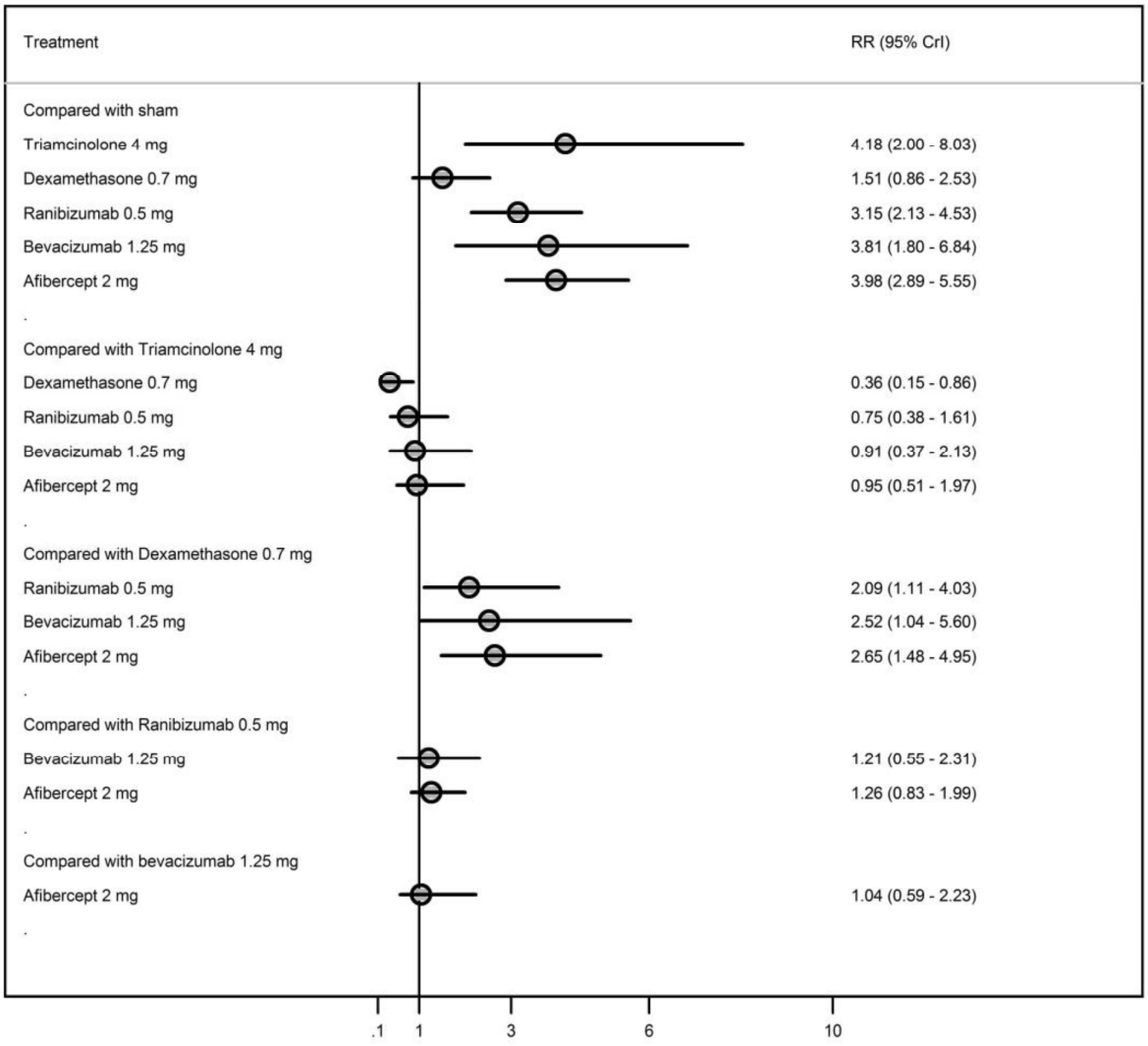


Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

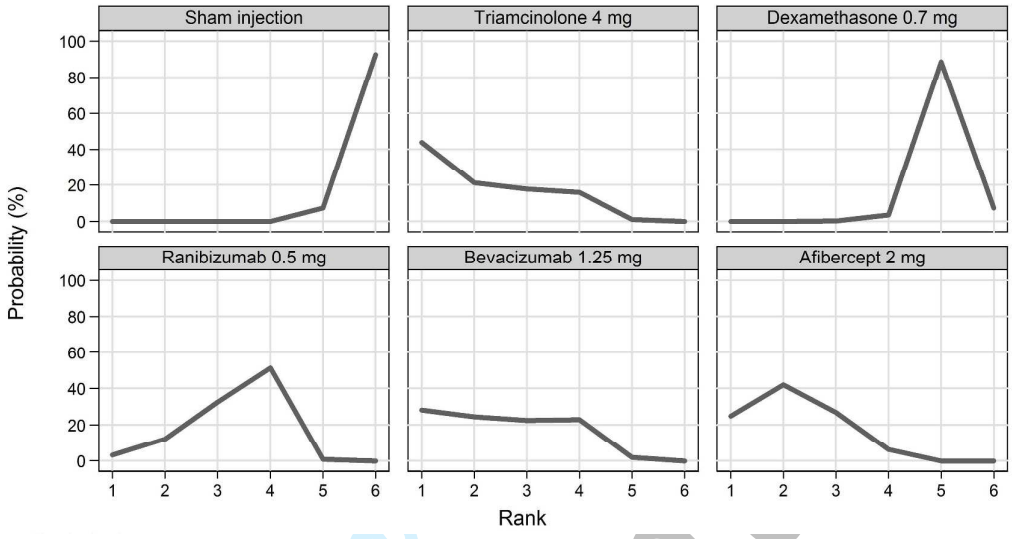


Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

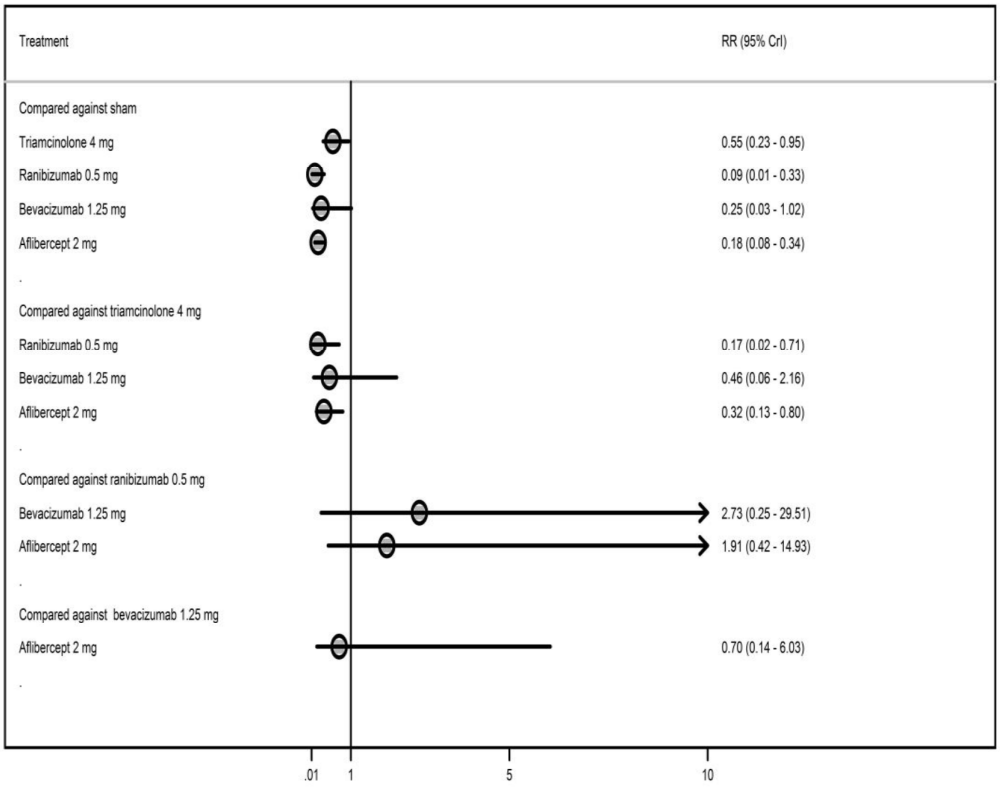


Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

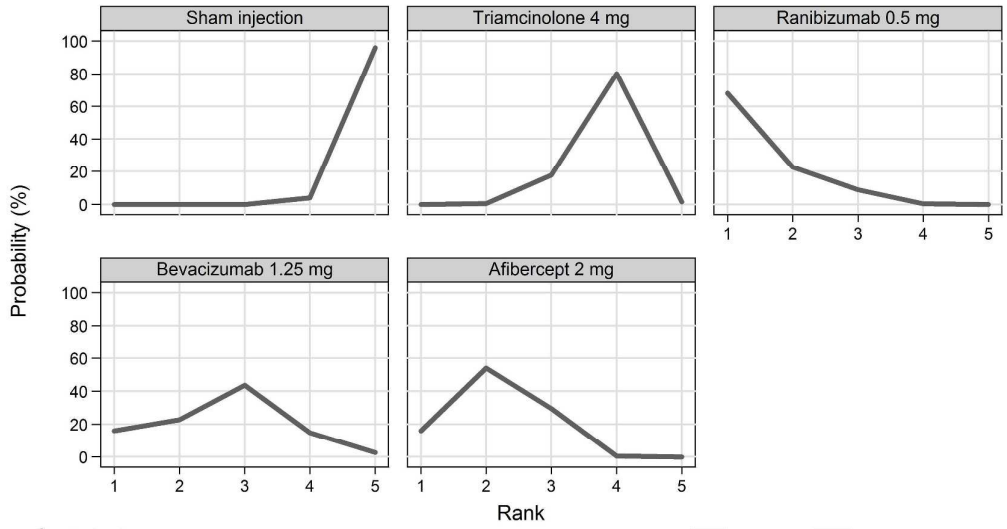


Figure 7: Mean BCVA change from baseline to 6 months.

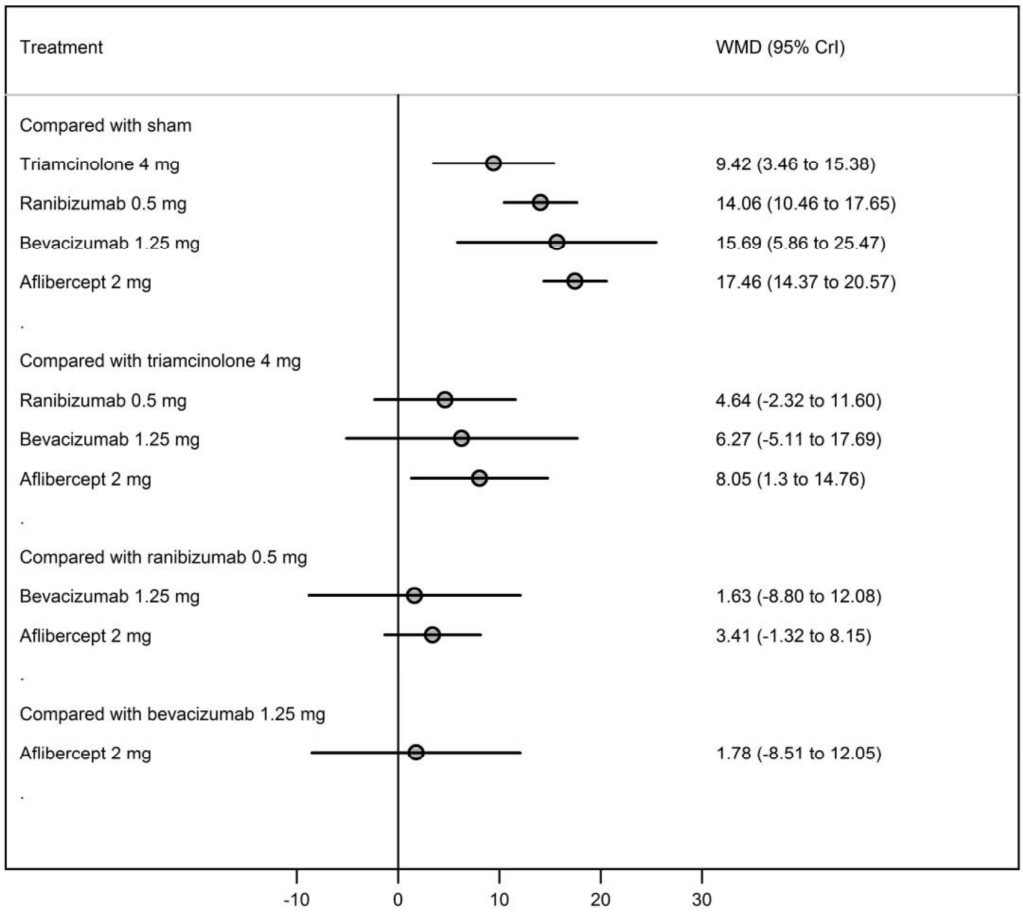
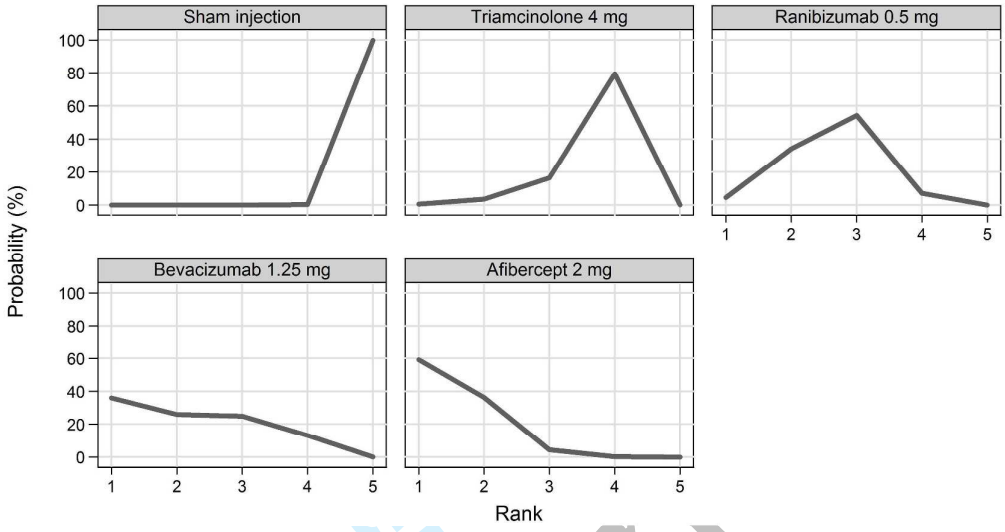


Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions



Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.
2 Retinal Vein Occlusion/
3 retinal vein occlusion.mp.
4 retinal vein obstruction.mp.
5 retinal venous occlusion.mp.
6 retinal venous obstruction.mp.
7 retina*.mp.
8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
9 7 and 8
10 1 or 2 or 3 or 4 or 5 or 6 or 9
11 randomized controlled trial.pt.
12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
13 11 or 12
14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
15 "systematic review*".tw.
16 meta analysis.pt.
17 14 or 15 or 16
18 10 and 13
19 10 and 17
20 18 or 19
21 limit 20 to yr="2005 -Current"

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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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Protocol – no published protocol exists for this study.

Word count: 3,331 words

What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone, ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] Therefore clinicians have three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms.[41]

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (Figure 4). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 5 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. Figure 6 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 7 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (Figure 8). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone, ranibizumab and aflibercept as options in the treatment of macular oedema secondary to CRVO[18-20]. Until these technologies are reviewed together and compared with each other, clinicians are left with three recommended drugs. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because it costs substantially less.[57] However the National Institute for Health and Care Excellence has not issued

guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Data Sharing Statement

No additional data available

Ethics approval – not required

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Figure Legend

Figure 1: study selection flow diagram

Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Figure 7: Mean BCVA change from baseline to 6 months.

Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

	Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months						
	Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA						
	Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-

Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

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What is already known on this subject

Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) and corticosteroids (dexamethasone and triamcinolone), given intravitreally, have all been shown to be effective compared to placebo for the treatment of macular oedema secondary to central retinal vein occlusion.

There are no head-to-head trials.

What this study adds

There was no evidence of a difference in the effectiveness of aflibercept, ranibizumab, bevacizumab and triamcinolone for improving vision.

Clinicians may prefer aflibercept because steroids are associated with cataract formation and ranibizumab might require more frequent injections.

Abstract

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis.

Design: Network meta-analysis

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science

Eligibility criteria for selecting studies: Only randomized controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining more than or equal to 3 lines, losing more than or equal to 3 lines, or mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian network meta-analysis was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab

1.25mg and aflibercept 2mg had a higher probability of improvement in mean best correct visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections

Systematic review registration – Not registered

Strengths and limitations of this study

- Important topic area, with significant policy implications
- Robust method used to identify studies
- Network meta-analysis are based on a number of assumptions
- Network meta-analysis is the best method to compare interventions in the absence of head to head trials

Introduction

Central retinal vein occlusion (CRVO) dramatically reduces an individual's functioning and quality of life.[1] It is estimated that the 15 year cumulative incidence of central retinal vein occlusion is 0.5%.[2] Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neo-vascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.[3] Cases with ischaemia carry a considerably worse prognosis as in around a third of them, neovascular glaucoma may develop; the most devastating complication of CRVO.[4]

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh and colleagues in a 27-year cohort study found that only 13% of people with CRVO were under 45 years of age.[3] In 95% of cases CRVO affects only one eye.[3] However visual loss in this already co-morbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with daily activities and become increasingly dependent on friends and family.[1]

For many years, laser photocoagulation was the only effective therapeutic strategy that could be used in the management of patients with CRVO. It was only useful for reducing the risk of neovascular glaucoma, but not effective for the treatment of macular oedema in CRVO.[5] Over the past decade a number of drugs to treat macular oedema have been introduced, including the steroids, triamcinolone and dexamethasone, and the anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and aflibercept. Dexamethasone,

ranibizumab and aflibercept have been assessed in large commercially funded trials.[6-13] Bevacizumab was originally developed as an anti-cancer drug and has been found to be effective in treating macular oedema secondary to age-related macular degeneration,[14] diabetic macular oedema, [15] branch retinal vein occlusion[16] and central retinal vein occlusion.[17] Like triamcinolone, bevacizumab is used off licence in the eye. Ranibizumab is a derived from the same parent molecule of the bevacizumab monoclonal antibody and was developed and commercially marketed specifically for use in the eye.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has recommended the use of dexamethasone, ranibizumab and aflibercept for the treatment of macular oedema secondary to CRVO in separate appraisals[18-20] Therefore clinicians have three NICE-recommended treatments for CRVO without head-to-head trials or clear guidance on which one may be best for their patients. On this basis, the aim of this study was to indirectly compare in a network meta-analysis the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone and triamcinolone for the treatment of macular oedema secondary to CRVO.

Methods

Information sources and search strategy

To identify suitable studies, initially for a systematic review of treatment of macular oedema after CRVO (submitted for publication) the following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). The MEDLINE search strategy is shown in appendix 1. This search strategy was modified for other databases. In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Study selection

Only randomised controlled trials which included patients with macular oedema secondary to central retinal vein occlusion were included. It was acceptable for a study to include both branch retinal vein occlusion and central retinal vein occlusion provided that the central retinal vein occlusion group was reported separately. The following drugs were included: dexamethasone, triamcinolone, ranibizumab, bevacizumab and aflibercept. Pegaptanib was not included because it is not used routinely in clinical practice. Only doses which are used in clinical practice were included. Studies had to report at least one of the following outcomes: proportions of patients gaining more than or equal to 3 lines from baseline to six months, proportions of patients losing more than or equal to 3 lines from baseline to six months and mean change in best corrected visual acuity (BCVA) from baseline to six months

Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used.[21] The trials were graded (unclear, high or low risk of bias) based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of outcome assessor, (iv) incomplete outcome data, and (v) selective outcome reporting.

Study selection and data abstraction

Two authors independently assessed the eligibility and methodological quality of the studies identified during the literature search. Two authors extracted and compared the data. For each study identified that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion. Studies were assessed for comparability based on the populations included, trial arms, outcome measures and duration of follow-up. Common comparators were identified from the trials and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative risk (RR) for the proportions of patients gaining more than or equal to 3 lines of vision, proportions of patients losing more than or equal to 3 lines of vision and weighted mean difference (WMD) for mean change BCVA. We used the following methods to calculate standard deviations, when incompletely reported: (1) contact with the corresponding author; or (2) estimation of the standard deviation on the basis of the sample size, median, and range as suggested by Hozo and colleagues[22] or on the basis of the sample size and P value.

In one trial (SCORE),[23-36] six month data was not available because patients were followed up every four months. For the dichotomous outcomes i.e. proportions of patients gaining and losing ≥3 lines, we averaged four and eight month data to get the six months follow-up data. For the third outcome i.e. mean change BCVA, again data from two time-points were used. Weighted mean and SDs for each treatment arm was calculated using mean and SDs of two time-points.

Data synthesis and model implementation

Bayesian network meta-analysis [37 38] (NMA) was used to compare the different interventions. Network meta-analysis is a generalization of meta-analysis methods because they allow comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% confidence intervals (95% CI). A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.[37 38]

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS 1.4.3.[39] Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool.[40] Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best, and so on, and presented the results graphically with rankograms.[41]

Like standard meta-analysis comparison, a NMA can be either a fixed- or a random-effect models. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed and random effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The fixed - effect model was chosen because of the small number of trials available for each comparison and difficulty in estimating between studies variance if random-effect model was implemented and the difference in DIC is less than 5.

Results

Study selection and characteristics

The literature search identified 945 articles, as shown in Figure 1. Seven studies were judged to be sufficiently comparable to be included in the network meta-analysis. Tables 1 and 2 present the characteristics and results of the included trials. Two studies [11-13] compared aflibercept 2 mg against sham; two identical studies [6-8] compared dexamethasone 0.7 mg (Ozurdex) against sham; one study [9 10] compared ranibizumab 0.5 mg against sham; one study [42-44]compared bevacizumab 1.25 mg against sham, and finally one study [23-36] compared triamcinolone 4 mg against observation. Sham or observation were used as the common comparator. The number of included participants varied from 60 [42-44] to 437 [6-8]. Most studies required patients to be treatment naive and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe onto the eye. All studies, except for Epstein and colleagues 2012[42-44], were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the network meta-analysis.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining more than or equal to 3 lines is shown in Figure 2. This network is the same for the other two outcomes, but without dexamethasone because the trial did not report these outcomes.

Risk of bias of included trials

Risk of bias is shown in Table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially

funded bevacizumab trial had fewer patients and inevitably results had wider confidence intervals.[42-44] In no study does it appear that patients were asked at the end of the trial what arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% credible interval in proportions of patients gaining more than or equal to 3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining more than or equal to 3 lines, triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of being more effective than a sham and dexamethasone (Figure 4). There was no difference in the proportions of patients gaining more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 5 displays forest plot of the risk ratio and 95% credible interval of proportions of patients losing more than or equal to 3 lines for all the possible pairwise comparisons. A smaller proportions of patients treated with triamcinolone 4mg, ranibizumab 0.5mg or aflibercept 2mg lost more than or equal to 3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing more than or equal to 3 lines between triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2mg. Figure 6 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 7 displays a forest plot of the mean changes and 95% credible intervals of

improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4mg, ranibizumab 0.5mg, bevacizumab 1.25mg, aflibercept 2mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4mg (Figure 8). There was no difference in mean change in BCVA from baseline between patients treated with ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2 mg.

Discussion

Statement of principal findings

Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of letters gained and mean change in BCVA. Dexamethasone was less effective compared to these drugs.

Strengths and limitations

This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction was used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere.[45] Five different drugs were suitable for network meta-analysis. Unpublished data was obtained from one author. [42-44] Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example Epstein 2012, assessing bevacizumab, only included 30 participants in each arm.[42-44] This resulted in wide credible intervals from the network meta-analysis which may lead to a type 1 error especially with regards to the proportions of patients losing more than or equal to 3 lines. The SCORE study compared triamcinolone to observation.[23-36] The NMA assumes a [11] similar effect of sham and observation and this may result in a small degree of bias. Only six months of data was included, and the long term effects are not known. Using a six-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by six months, benefits had been largely lost.[6-8]

As with most network meta-analyses, methodological heterogeneity was present. There were some differences amongst the trials. For example CRUISE[9 10], assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials.[12 13] There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers

No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone or dexamethasone have been published in central retinal vein occlusion. Part of the reason for this is that the Food and Drug Administration require proof of the safety and effectiveness of a drug.[46] The easiest and quickest method for pharmaceutical companies to produce this is through placebo controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example a comparison of ranibizumab and bevacizumab was undertaken in age related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT)[47] and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)[48] trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs.[49] Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein 2012.[42-44] In the CATT trial, more patients were

hospitalized in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab.[47] The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab.[50] Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2).[51] Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intra-ocular pressure and cataract formation.[6-8 23-36]These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may be already pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this has yet to be tested. The anti-VEFG drugs have a good safety profile and do not cause cataract formation.[9-13 42-44] For this reason are likely to be more favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity.[52] Initial results suggested that aflibercept would require fewer injections than ranibizumab.[51] Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age related macular degeneration. They found that 2 mg aflibercept administered every eight weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab every four weeks.[51] This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every two months following three initial monthly doses in age related macular

oedema.[53] This may be because aflibercept also appears to last longer in the eye than ranibizumab.[54] Age related macular degeneration is a more aggressive condition than central retinal vein occlusion and so it is unlikely that more frequent dosing would be needed. Therefore aflibercept may be preferred because it would reduce pressure on out-patient clinics. Furthermore there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.[55 56] This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects be any different for the macular oedema caused by central retinal vein occlusion. However we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone, ~~and~~ ranibizumab and aflibercept as options in the treatment of macular oedema secondary to CRVO ~~,~~[18 ~~-~~20 ~~19~~] ~~and is currently appraising aflibercept~~. Until these technologies are reviewed together and compared with each other, clinicians ~~may be~~are left with three recommended drugs ~~for macular oedema secondary to central retinal vein occlusion~~. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone.

Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at six months follow-up and with the dosing regimens in the trials. However these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove

more cost effective than both aflibercept and ranibizumab because it costs substantially less.[57] However the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

Unanswered questions and future research

Not all patients benefit from the use of anti-VEGF drugs; only about 60% gain 15 or more letters. It is not clear why some patients benefit more than others. Future research should focus on identifying subgroups of patients who are likely to benefit. Only a few of these trials included ischaemic patients, and in these trials only a few patients with ischaemia were included.[11-13] More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely-used EQ5D may not be sensitive enough to measure changes which are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of difference between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

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Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution statement

NW conceived the idea. All authors contributed to the design of the study. DS and OU undertook the statistical analysis. JF, DS and OU wrote the first draft of the manuscript. All authors redrafted and agreed the final article. JF is the guarantor.

Transparency statement

JF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Table 1: Baseline characteristics and results of all included studies

Study	Participants	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010[6-8] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Participants:** adults with visual acuity reduced because of macular oedema due to CRVO or BRVO	**1. Dexamethasone 0.7 mg (n=136)** Single dose **2. Dexamethasone 0.35 mg (n=154)** Single dose **3. Sham (n=147)** Single dose - a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

TRIAMCINOLONE		
SCORE 2009[23-36] USA **Setting:** multicentre **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months **Participants:** centre-involved macular oedema secondary to CRVO	**1. Triamcinolone 1 mg (n=92)** Every 4 months depending on retreatment regimen (ave 2.2 injections at 12 months) **2. Triamcinolone 4 mg (n=91)** Every 4 months depending on retreatment regimen (ave 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)) **3. Observation (n=88)** **Primary end point:** gain of ≥15 ETDRS letters
AFLIBERCEPT		
COPERNICUS 2012[12 13] International **Setting:** multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks **Participants:** adult patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=114)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=73)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

Field Code Changed

GALILEO 2012[11] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned up to 76 weeks	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Participants:** treatment-naïve patients with centre-involved CRVO for a maximum of 9 months	**1. Aflibercept 2mg (n=103)** Every 4 weeks for 6 months (ave number not available) **2. Sham (n=71)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to conjunctival surface) **Primary end point:** gain of ≥15 ETDRS letters

RANIBIZUMAB		
CRUISE 2010[9 10] USA **Setting:** multicentre **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months	**N:** 392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg), and 88.5% (sham) completed 6 months **Participants:** patients with foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months	**1. Ranibizumab 0.3 mg (n=132)** Every 4 weeks for 6 months (ave number not available) **2. Ranibizumab 0.5 mg (n=130)** Every 4 weeks for 6 months (ave number not available) **3. Sham (n=130)** Every 4 weeks for 6 months (ave number not available) (empty syringe without needle pressed to the injection site) **Primary end point:** mean change from baseline BCVA
BEVACIZUMAB		
Epstein 2012[42-44] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Participants:** patients with CRVO of ≤6 months	**1. Bevacizumab 1.25 mg (n=30)** Every 6 weeks for 6 months (ave number not available) **2. Sham (n=30)** Every 6 weeks for 6 months (ave number not available) (syringe without needle pressed to the globe) **Primary end point:** gain of ≥15 ETDRS letters

FU= follow-up, RCT = randomised controlled trial, N = number, CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, BRVO = branch retinal vein occlusion

Table 2: Baseline characteristics and results of included trials

	COPERNICUS[12 13]	GALILEO[11]	CRUISE[9 10]	GENEVA[6-8]	Epstein et al (2012)[42-44]	SCORE[23-36]
BASELINE SIMILARITIES						
Number (%) of patients						
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Dexa0.7 mg: 136 Sham: 147	Beva 1.25 mg: 30 Sham: 30	Triam 4 mg: 91 Obser: 88
Age (years)						
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 70.6 SD 12.6 Sham: 70.4 SD 10.4	Triam 4 mg: 67.5 SD 12.0 Obser: 69.2 SD 12.8
BCVA at baseline (SD)						
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 44.4 SD 15.3 Sham: 43.6 SD 16.0	Triam 4 mg: 51.0 SD 14.4 Obser: 52.1 SD 13.1
Duration of MO from diagnosis to screening						
	Aflib 2 mg: 2.73 SD3.09(in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 50.9 SD15.4)(in days) Sham: 87.6 SD79.1 (in days)	Rani 0.5 mg: - Sham: -	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: NR Sham: NR	Triam 4 mg: 4.2 SD 3.6 (in months) Obser: 4.2 SD 3.1 (in months)
RESULTS						
Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months						
	Aflib 2 mg: 64 (56.1)	Aflib 2 mg: 62 (60.2)	Rani 0.5 mg: 62 (47.7)	Dexa 0.7 mg: 25 (18)	Beva 1.25 mg: 18 (60%)	Triam 4 mg: 18 (19.5%) (avg of 4 and 8 mths)

	Sham: 9 (12.3)	Sham: 15 (22.1)	Sham: 22 (16.9)	Sham: 18 (12)	Sham: 6 (20%)	Obser: 3 (4%) (avg of 4 and 8 mths)
Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months						
	Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Dexa 0.7 mg: NR Sham: NR	Beva 1.25 mg: 2 (6.7%) Sham: 7 (23.3%)	Triam 4 mg: 19 (20.5%) (avg of 4 and 8 mths) Obser: 31 (35.5%) (avg of 4 and 8 mths)
Mean change (SD) from baseline in BCVA						
	Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)	Beva 1.25 mg: 14.1 SD 18.7 Sham: -2.0 SD 20.5	Triam 4 mg: -0.15 SD20.67 (n=85) (weight mean and SD of 4 and 8 months) Obser: -9.66 SD18.04 (n=75) (weighted mean and SD of 4 and 8 months)

NR = not reported, Aflib = aflibercept, Rani = ranibizumab, Dexa = dexamethasone, Triam = triamcinolone, Obser = observation, SD = standard deviation, avg = average

Table 3: Risk of bias

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GENEVA 2010[6-8]	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
SCORE 2009[23-36]	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan
COPERNICUS 2012[12 13]	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
GALILEO 2012[11]	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

CRUISE 2010[9 10]	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.
Epstein 2012[42-44]	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

ITT= intention to treat, FU = follow-up

Figure Legend

Figure 1: study selection flow diagram

Figure 2: Network of randomized controlled trials comparing different treatments for proportions of gaining 3 or more lines of vision

Figure 3: Proportions of patients gaining 3 lines or more from baseline to six months

Figure 4: Rankogram for gaining ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Figure 5: Proportions of patients losing 3 lines or more from baseline to six months

Figure 6: Rankogram for losing ≥3 lines - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Figure 7: Mean BCVA change from baseline to 6 months.

Figure 8: Rankogram for mean change in BCVA - distribution of the probabilities of every treatment being ranked at each of the possible 6 positions

Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.
2 Retinal Vein Occlusion/
3 retinal vein occlusion.mp.
4 retinal vein obstruction.mp.
5 retinal venous occlusion.mp.
6 retinal venous obstruction.mp.
7 retina*.mp.
8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
9 7 and 8
10 1 or 2 or 3 or 4 or 5 or 6 or 9
11 randomized controlled trial.pt.
12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
13 11 or 12
14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
15 "systematic review*".tw.
16 meta analysis.pt.
17 14 or 15 or 16
18 10 and 13
19 10 and 17
20 18 or 19
21 limit 20 to yr="2005 -Current"

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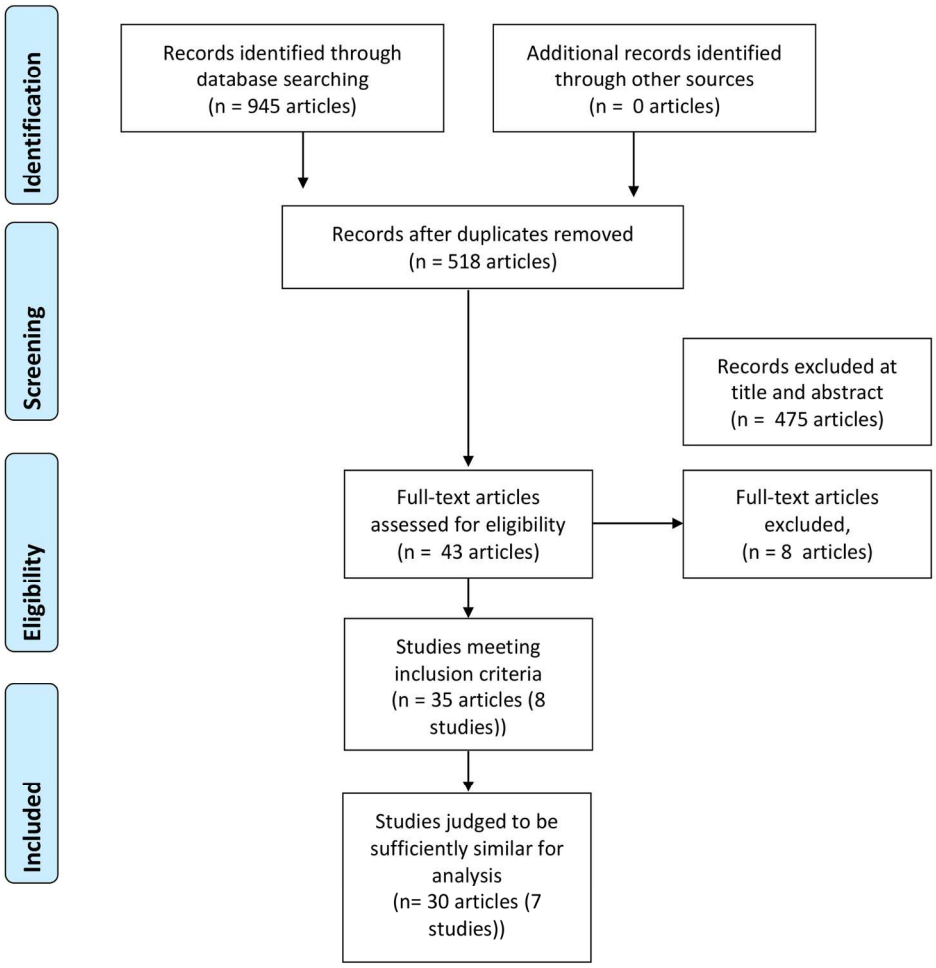

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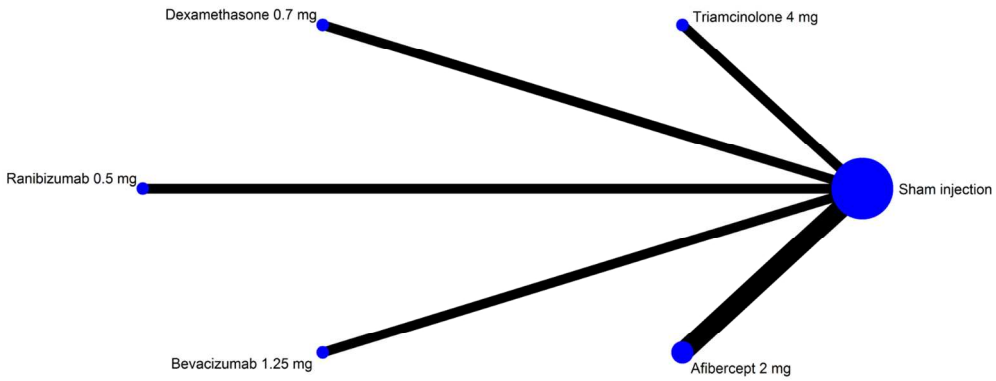

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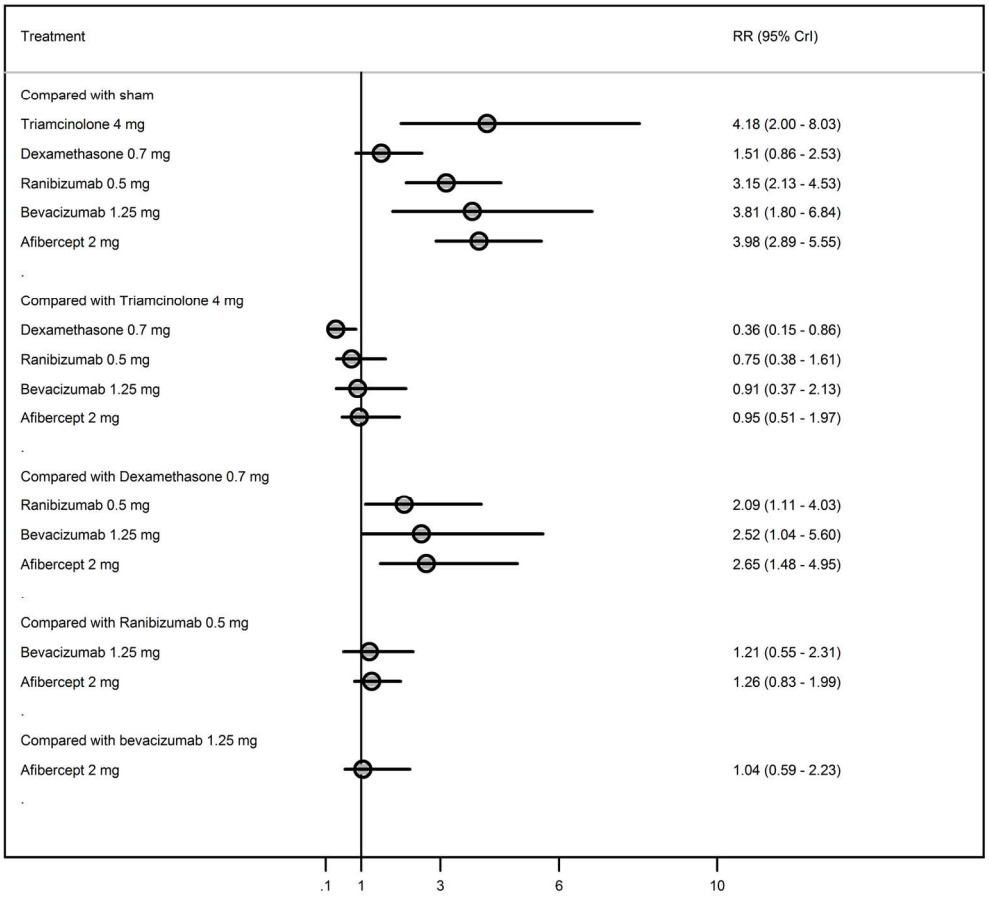

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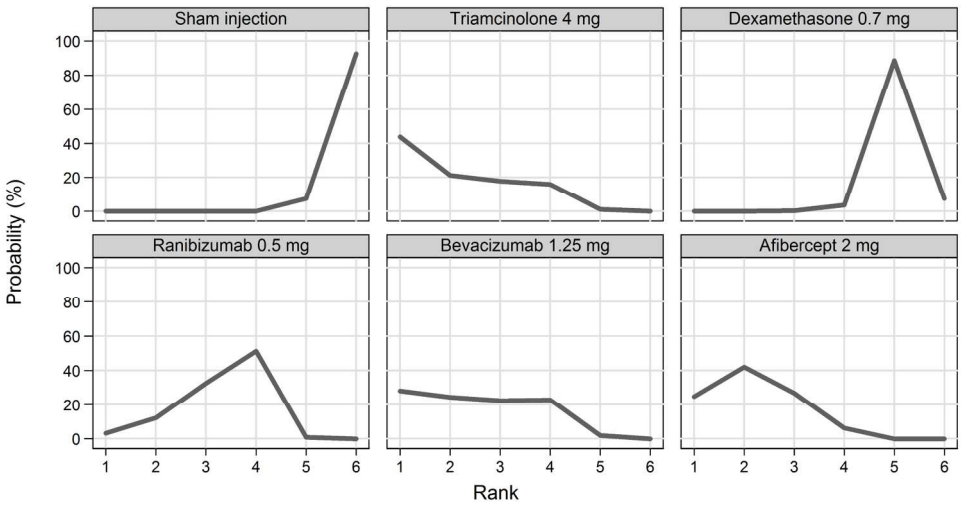

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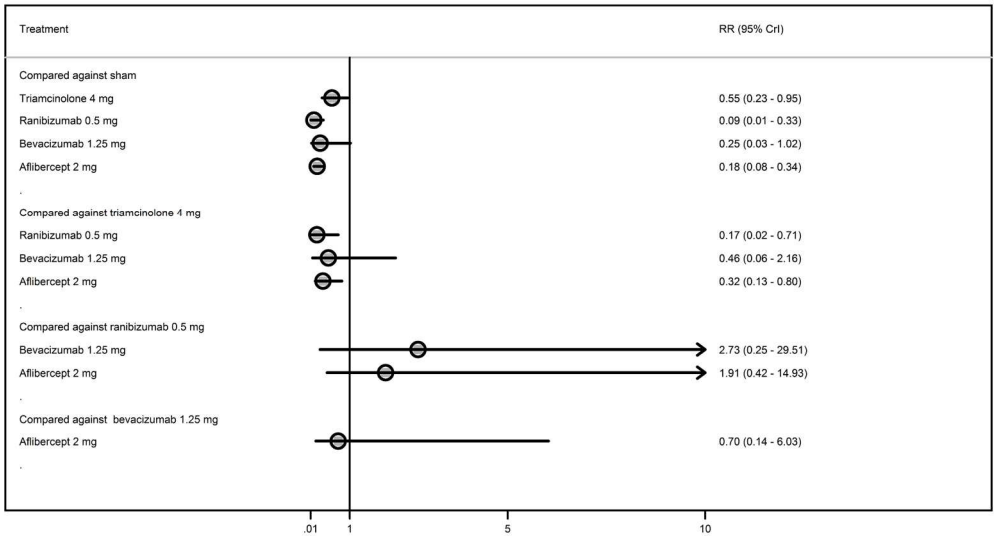

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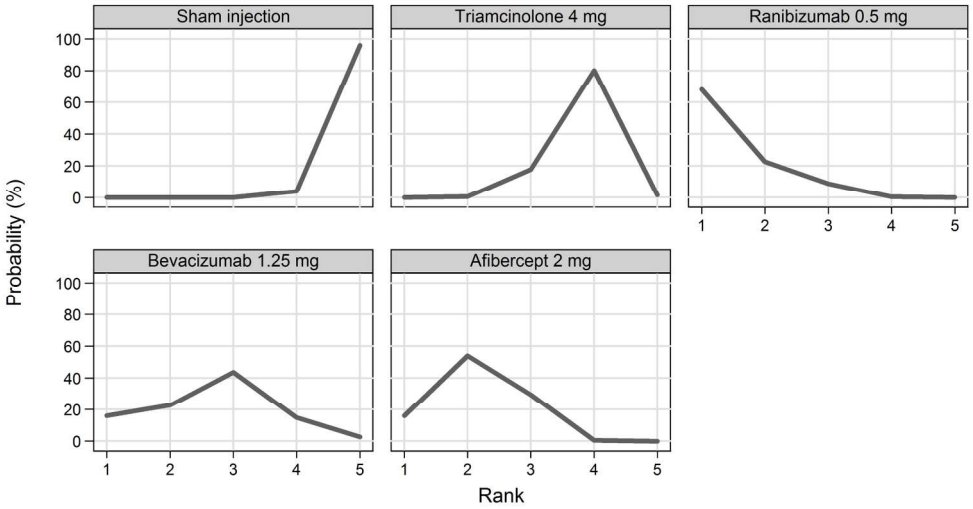

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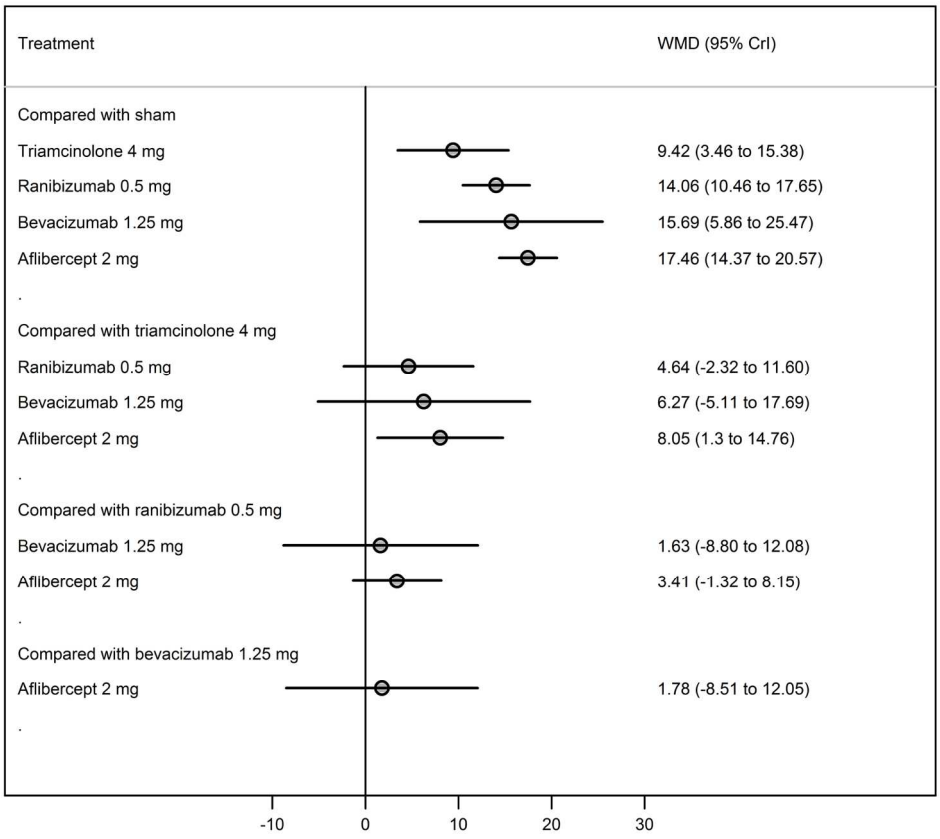

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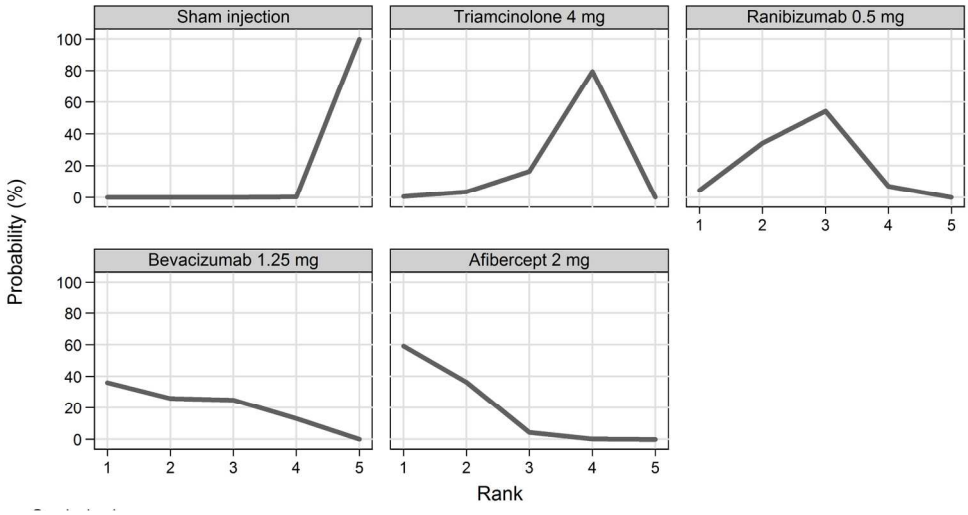

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Appendix: MEDLINE search strategy

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.

2 Retinal Vein Occlusion/

3 retinal vein occlusion.mp.

4 retinal vein obstruction.mp.

5 retinal venous occlusion.mp.

6 retinal venous obstruction.mp.

7 retina*.mp.

8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

9 7 and 8

10 1 or 2 or 3 or 4 or 5 or 6 or 9

11 randomized controlled trial.pt.

12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

13 11 or 12

14 (metaanalys* or "meta analys*" or "meta-analys*").tw.

15 "systematic review*".tw.

16 meta analysis.pt.

17 14 or 15 or 16

18 10 and 13

19 10 and 17

20 18 or 19

21 limit 20 to yr="2005 -Current"

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	41
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11+27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25-26
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	29-31
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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